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**Ellis, Calvin C., Wooldridge, Wilfred E., and Weiss, Richard S.: The Journal of Investigative Dermatology, Vol. 10, No. 6, June 1948*

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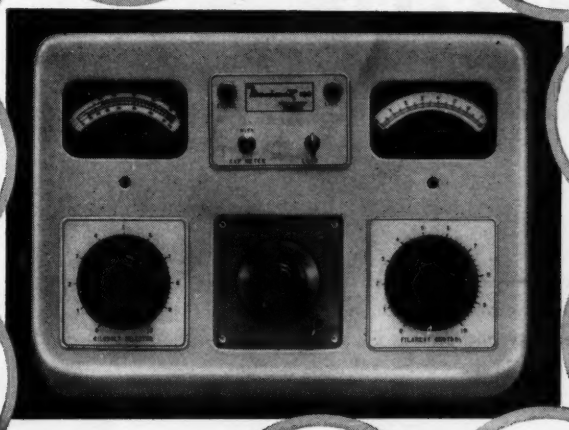

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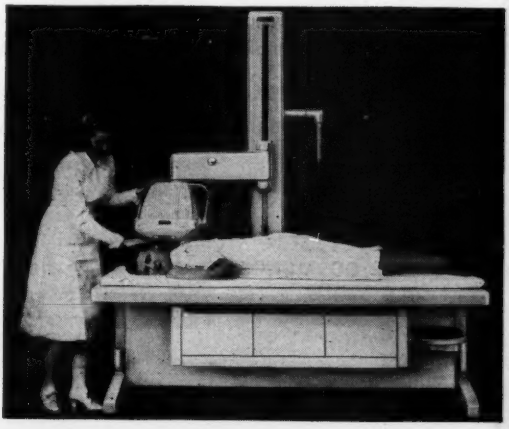

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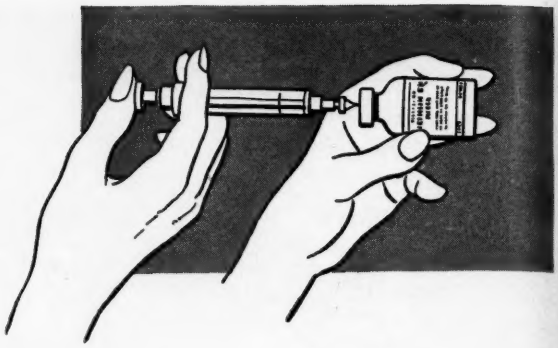

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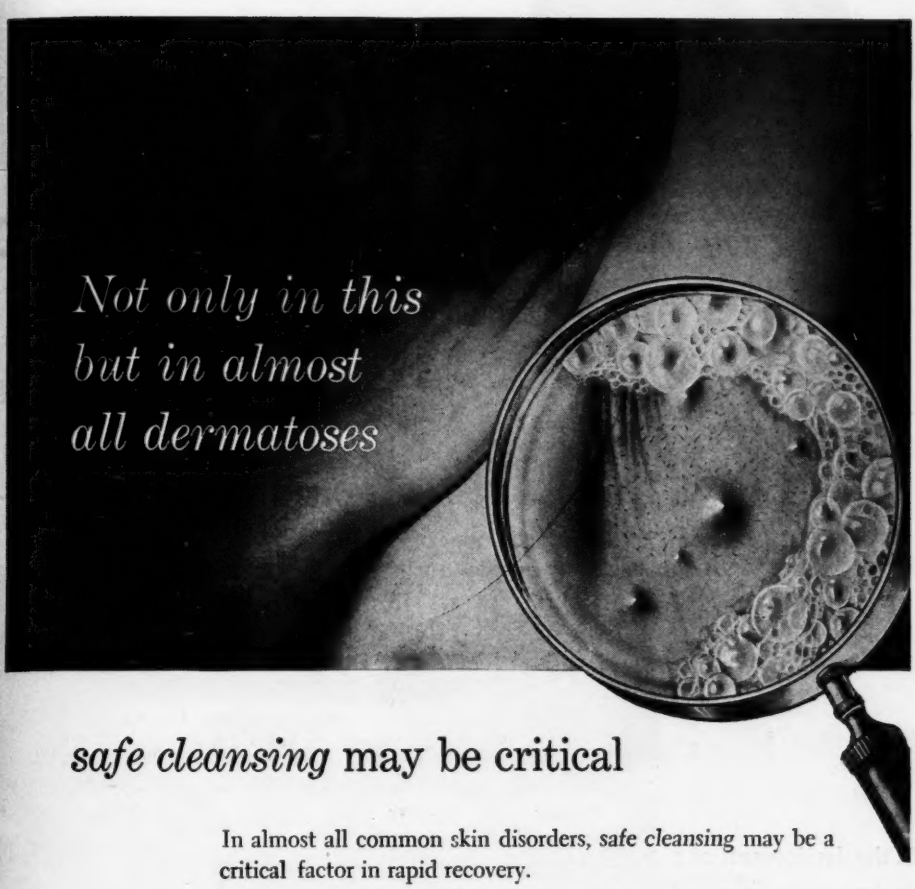

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1. Sulzberger, M. B., and Baer, R. L.: in Medical Uses of Soap. Philadelphia, J. B. Lippincott Co., 1945, pp. 62, 65.

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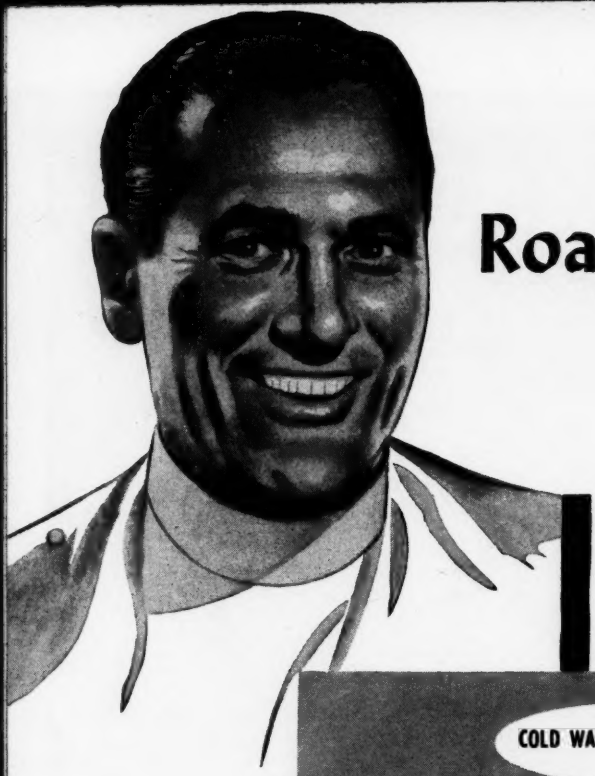

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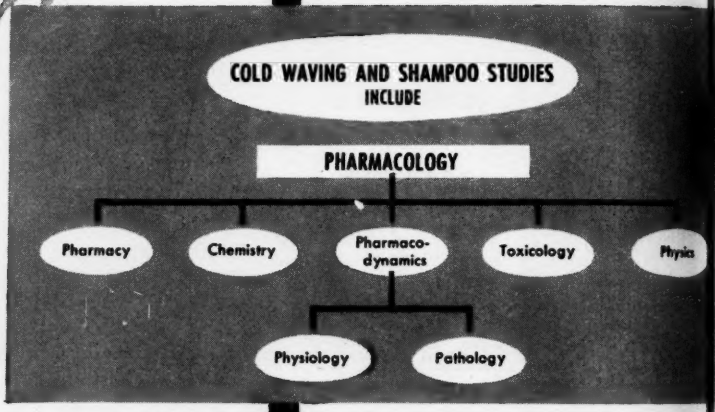

In the development of a netic, the scientists involved re concerned not only with cosmetic effects of the product, but also with the iological actions, absorption, fate and excretion of e components of the product.

In such considerations, the cosmetic is investigated though it were a drug, and the cosmetic chemist s seriously involved in many scientific fields which fall within the scope of pharmacology.

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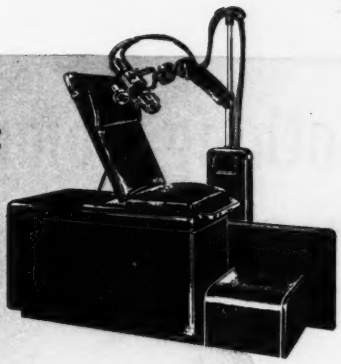

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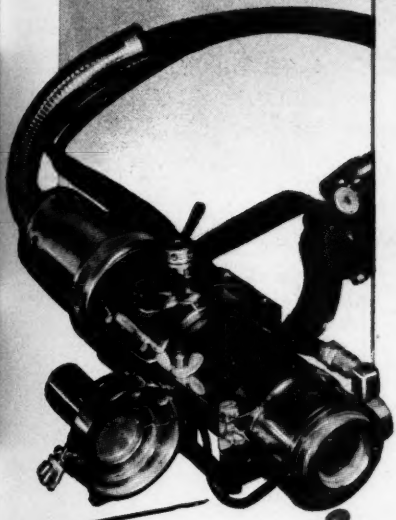

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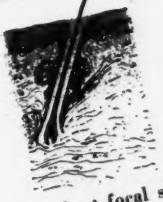

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A. M. A.
Archives of Dermatology and Syphilology

VOLUME 62 DECEMBER 1950 NUMBER 6

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STUDIES ON THE L. E. PHENOMENON

SETH S. BARNES, M.D.
THOMAS W. MOFFATT, M.D.
CLINTON W. LANE, M.D.
AND
RICHARD S. WEISS, M.D.
ST. LOUIS

IN JANUARY 1948 Hargraves and his associates [1] first reported observations on certain bone marrow elements to which they gave the name L. E cells and tart cells. In September of that same year Haserick and Sundberg [2] reported further observations on the L. E. cell. In February 1949 Sundberg and Lick [3] reported for the first time the observation of the L. E. cell in peripheral blood, and this observation was confirmed by Hargraves [4] in April 1949. In May 1949 Klemperer and his co-workers [5] reported the observation of hematoxylin-staining bodies comparable to L. E. bodies in 31 autopsies of acute disseminate

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., June 22, 1950.

Studies, observations and reports from the Dermatological Departments of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, service of Richard S. Weiss, M.D.

1. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of Two Bone Marrow Elements: The "Tart" Cell and the "L. E." Cell, Proc. Staff Meet., Mayo Clin. **23**:25-28 (Jan. 21) 1948.

2. Haserick, J. R., and Sundberg, R. D.: The Bone Marrow as a Diagnostic Aid in Acute Disseminated Lupus Erythematosus: Report on Hargraves' "L. E." Cell, J. Invest. Dermat. **11**:209-213 (Sept.) 1948.

3. Sundberg, R. D., and Lick, N. B.: "L. E." Cells in the Blood in Acute Disseminated Lupus Erythematosus, J. Invest. Dermat. **12**:83-84 (Feb.) 1949.

4. Hargraves, M. M.: Production in Vitro of the "L. E." Cell Phenomenon: Use of Normal Bone Marrow Elements and Blood Plasma from Patients with Acute Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **24**:234-237 (April 27) 1949.

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lupus erythematosus patients. In July 1949 Haserick and Bortz [6] reported that they had produced L. E. cells by mixing the plasma of acute disseminate lupus erythematosus patients and normal sternal marrow. In April 1950 Moffatt, Barnes and Weiss [7] described a method of producing the L. E. cells by use of the plasma of acute lupus erythematosus patients mixed with the white cells obtained by centrifugation of blood from normal persons. The same authors [8] reported a method of demonstrating the L. E. phenomenon without the use of anticoagulants. Madden,[9] in a paper read before the American Dermatological Association in 1949, stated that Hargraves cells were found only in patients with acute disseminate lupus erythematosus and that the number of these cells decreased as the systemic symptoms subsided.

It is our purpose in this paper to summarize the work that we have done on the L. E. cell and demonstrate the present status of the L. E. phenomenon by means of photographs and charts.

The tart cell and the L. E. cell were first described in Hargraves' original paper. The former was described as a histiocyte or a "monocytoid reticuloendothelial cell" that contains a second characteristic nucleus placed in the *Hof* of the primary nucleus. This second nucleus stains a reddish purple with Wright's stain and possesses a distinct chromatin pattern. This cell occurs infrequently in normal marrow and with somewhat greater frequency in the marrow of persons ill with various diseases. In our work we have encountered few cells of this description.

The typical L. E. cell is a mature neutrophilic leukocyte which contains within its cell membrane one or more masses of nuclear material. These masses, round or oval in outline, vary in size from a third of the size of a red blood cell to three or four times that size. For convenience they may be called L. E. bodies. They vary in appearance from granular to smoky to homogeneous. The chromatin network which distinguishes nuclei of cells is absent. Ordinarily these bodies take a bluish stain, although there is variation in the staining from bluish to purple or

6. Haserick, J. R., and Bortz, D. W.: Normal Bone Marrow Inclusion Phenomenon Induced by Lupus Erythematosus Plasma, J. Invest. Dermat. **13**:47-50 (Aug.) 1949.

7. Moffatt, T. W.; Barnes, S. S., and Weiss, R. S.: The Induction of the L. E. Cell (Hargraves) in Normal Peripheral Blood, J. Invest. Dermat. **14**:153-156 (March) 1950.

8. Barnes, S. S.; Moffatt, T. W., and Weiss, R. S.: Demonstration of the L. E. Cell in the Absence of Anticoagulant, J. Invest. Dermat. **14**:397-400 (June) 1950.

9. Madden, J. F.: Comparison of Muscle Biopsies and Bone Marrow Examinations in Dermatomyositis and Lupus Erythematosus, Arch. Dermat & Syph. **62**:192-205 (Aug.) 1950.

reddish brown. A characteristic picture is formed when an L. E. body of large dimension is present within a cell. It is usually seen as a large round bluish homogeneous body with darker-staining lobulated cell nuclei festooning its periphery. A thin outer rim of cell cytoplasm completes the picture.

In addition to the L. E. cells the L. E. phenomenon includes the formation of clumps and rosettes. The rosette consists of a central mass of bluish-staining cell debris surrounded by phagocytes forming a ring around the central mass. The phagocytes appear to be engulfing the material in the center. Lysis of leukocytes from a moderate to a pronounced degree is uniformly present in these smears. Notable also is the abundance of dark-staining particles which appear to cling to the

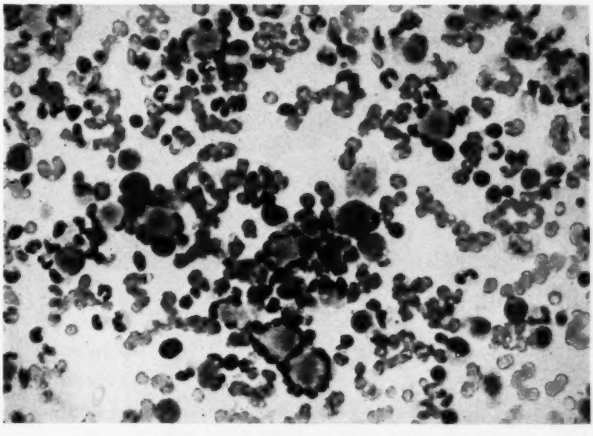

Fig.1.—The L. E. cell in sternal marrow from a patient with acute disseminated lupus erythematosus (marrow heparinized).

outer cell membrane of the phagocyte. Hargraves believed these particles to be fragmented nuclear material.

DEMONSTRATION OF THE L. E. CELL

Using the Hargraves' technic, we have demonstrated the L. E. cell in the sternal marrow from patients ill with subacute and acute disseminate lupus erythematosus.

In only two cases have we found the L. E. cell in the peripheral blood of patients ill with acute disseminate lupus erythematosus, using the method of Sundberg and Lick. It is a long and tedious process.

We have mixed the plasma from heparinized peripheral blood of acute lupus erythematosus patients with heparinized normal sternal

marrow and obtained L. E. cells consistently, verifying the work of Haserick and Bortz. This procedure was done with plasma from two patients, and we consider it to be a good method.

We have been successful in inducing L. E. cells in normal peripheral blood to which anticoagulant (heparin) was added. The plasma of a patient with acute lupus erythematosus mixed with buffy coat of centrifuged heparinized blood of a normal person produced the L. E. phenomenon.[7]

EXPERIMENTAL RESULTS

The sternal marrow of six patients with acute disseminated lupus erythematosus was positive for the L. E. phenomenon. In four of these

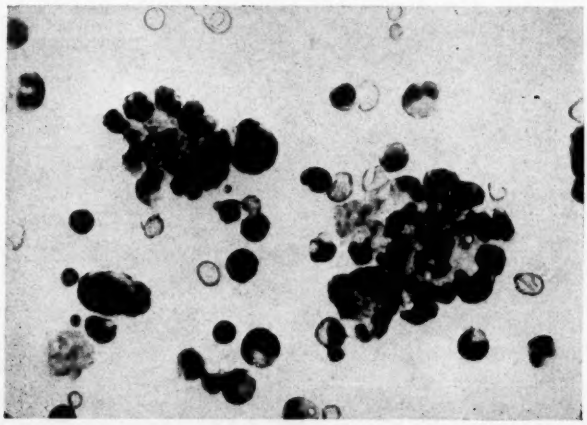

Fig. 2.—The L. E. cell produced in normal human sternal marrow by adding plasma from heparinized blood of acute lupus erythematosus patients.

the blood serum also gave a positive reaction. (Two of these patients whose sternal marrow was examined did not have serum examinations).

The blood serum of 15 patients gave a positive reaction to the test. Four of these patients also had the L. E. cell in their sternal marrow.

The blood serum of two patients in whom the disease was in remission gave a negative reaction to the test.

The sternal marrow of 10 patients with subacute disseminated lupus erythematosus gave a negative reaction.

The blood serum of six patients with the subacute form of the disease gave positive reactions, although many examinations were necessary in some of these patients to get these positive results.

The blood serum of 14 patients with subacute disseminated lupus erythematosus reacted negatively.

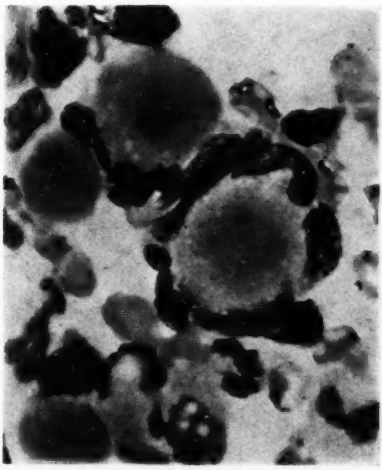

Fig. 3.—The L. E. phenomenon (clumping, rosette and the L. E. cell), produced by adding blood serum from a patient with acute disseminate lupus erythematosus to normal white blood cells (the Barnes-Moffatt test).

TABLE 1.—*Observations in Cases of Acute Disseminate Lupus Erythematosus*

Case No.	Patient	Sex	Result of Sternal Marrow Examination for L. E. Cells	Result of Blood Serum Examination for L. E. Cells
1	J. W.	F	Positive	No examination
2	M. W.	F	Positive	Positive
3	E. A.	F	Positive	Positive
4	P. B.	F	Positive	Positive
5	S.	F	Positive	Positive (confirmed at autopsy)
6	M. K.	F	No examination	Positive (confirmed at autopsy)
7	D. F.	F	Positive	No examination (confirmed at autopsy)
8	L. S.	F	No examination	Positive
9	J. T.	F	No examination	Positive
10	E. G.	F	No examination	Positive
11	W. H. L.	M	No examination	Positive
12	A. S.	M	No examination	Positive
13	H. W.	F	No examination	Positive
14	H. A.	M	No examination	Positive
15	J. McM.	M	No examination	Positive
16	R. G.	F	No examination	Positive
17	S.	F	No examination	Positive (confirmed at autopsy)

TABLE. 2.—*Observations in Cases of Acute Disseminate Lupus Erythematosus, in Remission*

Case No.	Patient	Sex	Result of Sternal Marrow Examination for L. E. Cells	Result of Blood Serum Examination for L. E. Cells
1	E. L.	F	No examination	Negative
2	F. D. H.	F	No examination	Negative

TABLE 3.—*Observations in Cases of Subacute Disseminate Lupus Erythematosus*

Case No.	Patient	Sex	Result of Sternal Marrow Examination for L. E. Cells	Result of Blood Serum Examination for L. E. Cells
1	P. L.	F	No examination	Positive
2	M. A.	F	Negative	Positive
3	G. R.	F	No examination	Positive
4	F. T.	F	Negative	Negative
5	J. A.	M	Negative	Negative
6	A. R.	M	Negative	Negative
7	W.	F	Negative	Negative
8	H.	M	Negative	Negative
9	T.	F	Negative	Negative
10	K. P.	F	Negative	Negative
11	H.	F	No examination	Negative
12	M. S.	F	No examination	Positive
13	J. W.	M	No examination	Negative
14	T. H.	M	Negative	Negative
15	J. I.	F	No examination	Negative
16	D. I.	F	No examination	Positive
17	A. S.	M	No examination	Positive
18	J. P.	F	Negative	Negative
19	R. P.	F	No examination	Negative
20	F. B.	F	No examination	Negative

In no patient with subacute lupus erythematosus was the sternal marrow reaction positive (10 cases studied). One patient had a negative sternal marrow and a positive blood serum reaction. Nine patients had negative sternal marrow and blood serum reactions.

Two patients with chronic disseminated lupus erythematosus showed negative reactions to marrow and serum tests.

Three patients with chronic discoid lupus erythematosus gave negative reaction to marrow and serum tests.

CONTROLS

We present in table 6 the results of studies made on sternal marrow and blood of patients who did not have lupus erythematosus but did have

TABLE 4.—*Observations in Cases of Chronic Disseminate Lupus Erythematosus*

Case No.	Patient	Sex	Result of Sternal Marrow Examination for L. E. Cells	Result of Blood Serum Examination for L. E. Cells
1	N. R. M.	F	Negative	Negative
2	O. B.	F	No examination	Negative

TABLE 5.—*Observations in Cases of Chronic Discoid Lupus Erythematosus*

Case No.	Patient	Sex	Result of Sternal Marrow Examination for L. E. Cells	Result of Blood Serum Examination for L. E. Cells
1	C. M.	M	Negative	Negative
2	D. K.	F	Negative	Negative
3	J. A.	M	Negative	Negative

various diseases of the so-called collagen group. Persons with numerous other diseases characterized by severe toxic phenomena were also tested. In none of these patients were we able to demonstrate the L. E. phenomenon. It will be noted that the table includes observations on blood from numerous patients with high serum globulin levels.

The sternal marrow and blood serum specimens of 92 control patients were examined (69 sternal marrow and 92 blood serum samples). Not a single positive result was encountered (see table 6). This list includes four cases of dermatomyositis, four cases of diffuse scleroderma, three cases of rheumatoid arthritis, two cases of multiple myeloma, three cases of hepatic cirrhosis with hyperglobulinemia, two cases of mycosis fungoides, one case of systemic sarcoidosis, one case of Hodgkin's disease and many others, as can be seen in table 6. In 19 cases of undiagnosed fevers and eruptions there were negative test reactions.

ANTICOAGULANT

It has been suggested that the L. E. phenomenon might be an artefact associated in some way with anticoagulant. In all the investigations reported up to this time, an anticoagulant had been utilized. We have

TABLE 6.—*Observations on Control Patients*

Diagnosis	No. Examined	Result of Sternal Marrow Examination for L. E. Cells	Result of Blood Serum Examination for L. E. Cells
Dermatomyositis	4	3 negative, 1 not examined	4 negative
Diffuse scleroderma	4	4 negative	4 negative
Rheumatoid arthritis	3	3 negative	3 negative
Nodular vasculitis	2	2 negative	2 negative
Periarteritis nodosa	1	Not examined	1 negative
Multiple myeloma	2	2 negative	2 negative
Hepatic cirrhosis with high amount of globulin	3	3 negative	3 negative
Syphilis with high Kahn titer	3	3 negative	3 negative
Kaposi's varicelliform eruption	2	2 negative	2 negative
Pemphigus chronicus vulgaris	3	3 negative	3 negative
Pemphigus foliaceus	1	1 negative	1 negative
Mycosis fungoides	2	2 negative	2 negative
Lymphosarcoma	1	1 negative	1 negative
Hodgkin's disease	1	1 negative	1 negative
Acute leukemia	1	Not examined	1 negative
Chronic lymphogenous leukemia	1	1 negative	1 negative
Sarcoidosis, systemic	1	1 negative	1 negative
Poikiloderma atrophicans vasculare	1	1 negative	1 negative
Chronic glomerulonephritis	1	1 negative	1 negative
Chronic pyelonephritis	1	Not examined	1 negative
Pneumonia, organizing	1	Not examined	1 negative
Arteriosclerosis, advanced	1	Not examined	1 negative
Multiple hemangiomas	1	Not examined	1 negative
Raynaud's disease	1	1 negative	1 negative
Carcinomas	21	11 negative, 10 not examined	21 negative
Pseudocyst of pancreas	1	1 negative	1 negative
Seborrheic dermatitis	1	1 negative	1 negative
Generalized exfoliative dermatitis	4	3 negative, 1 not examined	4 negative
Hand eczema, contact origin	1	1 negative	1 negative
Stasis dermatitis of extremities	2	2 negative	2 negative
Pulmonary blastomycosis	1	1 negative	1 negative
Undiagnosed eruptions and fevers	19	9 negative, 10 not examined	19 negative
Totals	92	69	92

published a recent paper with an account of a second technic [8] by means of which we have succeeded in demonstrating the L. E. cell in the absence of anticoagulant or added material of any sort.[10] Briefly, in this technic

10. Recently Harry Agress (personal communication to the authors) demonstrated L. E. cells and intracellular and extracellular bodies in fixed sections of clotted sternal marrow obtained from a patient with acute lupus erythematosus. No anticoagulant was used.

the serum from clotted peripheral blood from the acute lupus erythematosus patient is mixed with buffy coat from normal blood that has been defibrinated by stirring with a sterile applicator. The fibrin is removed, and then the defibrinated blood is centrifuged and the buffy coat pipetted off. Sterile conditions should be maintained.

HITHERTO UNDESCRIBED INCLUSION BODIES

We have recently noted oval intracellular bodies of a unique type located, for the most part, in the cytoplasmic or nuclear portion of neu-

Fig. 4.—Oval inclusion body (arrow) in a leukocyte, which may represent a stage in the evolution of the L. E. body.

trophilic leukocytes. They appeared to be composed of dark-staining granular material with a darker or polychromatic-staining dot in the center resembling a nucleolus within a nucleus. The oval body was ringed with a halo of clear material. There is some evidence that these granular bodies may represent stages in the evolution of the L. E. body.

COMMENTS

Our work seems to indicate that the L. E. phenomenon can be demonstrated invariably in acute lupus erythematosus in the active stage and occasionally in the subacute form. The L. E. cells are observed in

greatest abundance during the acute phase of the illness and tend to decrease in numbers or completely disappear during remissions.

Serum from patients with chronic discoid or disseminate discoid lupus erythematosus does not produce the L. E. phenomenon.

Other diseases of the so-called collagen group do not produce the L. E. phenomenon.

Hargraves reported the observation of the L. E. cell in one case of multiple myeloma. We have studied two cases of this disease; in one there was no evidence of the L. E. phenomenon, and in the other there was a moderate amount of lysis and clumping of leukocytes. After a very careful and prolonged search a few cells with morphologic features resembling L. E. cells were detected; however, on close inspection and study these cells were found to have retained all the characteristic staining properties of cell nuclei, including the chromatin network. They could not be identified as L. E. cells.

In diseases showing high globulinemia and reversal of the albumin-globulin ratio similar to that shown in acute lupus erythematosus L. E. cells were not demonstrated in the sternal marrow and the reaction to the Barnes-Moffatt test was not positive.

Because a false reaction to the serologic test for syphilis often accompanies acute lupus erythematosus, several samples of high titer syphilitic blood were tested; they failed to show the L. E. phenomenon.

In one of our cases of acute disseminate lupus erythematosus an early sternal marrow examination failed to show the L. E. cells. Two weeks later the peripheral blood test revealed L. E. cells, and after the sternal puncture was repeated the marrow was shown to be loaded with L. E. cells.

We believe that the L. E. phenomenon is a constant observation in acute lupus erythematosus in the active stage and that the two tests which we have described by which L. E. cells may be induced in normal leukocytes constitute a helpful diagnostic procedure. The tests may be particularly useful in acute disseminate lupus erythematosus in which no skin eruption is present.

We suggest that the oval bodies which we have described may prove to be stages in the development of the L. E. body.

Further study is necessary concerning the identification of these oval bodies and the genesis of the L. E. cell.

STAINING METHODS

We include here the staining methods which we have used in demonstrating the L. E. phenomenon and the oval bodies.

1. Withdraw 10 to 15 cc. of venous blood in a sterile syringe. Empty blood from the syringe into a sterile 20 cc. test tube. Place this test tube in an upright

position, and allow a normal retractile clot to form. If the blood specimen is to be preserved the test tube should be tightly corked and sealed and refrigerated.

2. Withdraw 10 to 15 cc. of venous blood from a healthy normal person. Empty blood from the syringe into a sterile 20 cc. test tube. Defibrinate this blood by stirring it for at least 10 minutes with sterile applicator sticks. Discard the sticks with adherent fibrin. Centrifuge the defibrinated blood at 2,000 r.p.m. for five minutes. Pipet off the serum layer, leaving the buffy coat layer on the surface. If the test tube is slanted the buffy coat may be readily removed with a capillary pipet.

3. Place approximately 10 drops of test serum and approximately 10 drops of buffy coat together, using sterile capillary pipets, in a sterile Kahn dilution tube. Leave the mixture in the tube, agitating it gently every few minutes for 20 minutes. The formation of L. E. cells takes place at ordinary room temperature but seems to be accelerated at higher temperatures up to 37 C. (98.6 F.), or body temperature.

4. Remove the mixture from the Kahn dilution tube with a sterile capillary pipet and place in a sterile Wintrobe (hematocrit) tube. Centrifuge this tube at 2,000 r.p.m. for five minutes. Using the capillary pipet, discard the serum layer. Gently lift off the buffy coat, and drop it on several clean glass slides. Smear the slides quickly, and wave them through the air to dry them rapidly.

5. Cover each slide with 15 to 20 drops of Wright's stain. After 90 seconds cover the slides with a buffer for Wright's stain for two minutes. Dump this buffer off the slides, and cover them with diluted Giemsa stain.[11] Leave the diluted Giemsa stain on the slides for six minutes. Wash them with distilled water and dry.

SUMMARY

The work of previous investigators has been repeated and their results confirmed.

The results of our investigation of the L. E. phenomenon have been presented and methods outlined for a relatively simple test for the demonstration of this phenomenon.

The L. E. phenomenon, in our opinion, does not depend on the addition of anticoagulant, as we have demonstrated its presence in the absence of anticoagulant.

A preliminary report is submitted on the observation of a hitherto unreported body in leukocytes exposed to disseminated lupus erythematosus serum.

CONCLUSIONS

The L. E. phenomenon appears to be specific.

When the L. E. phenomenon is absent acute lupus erythematosus is not excluded but is unlikely.

In patients with so-called "fever of unknown origin" this test may give useful information.

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11. The diluted Giemsa stain must be freshly prepared. Use 3 cc. of Wright's buffer and 9 drops of Giemsa stain for each slide stained, mixing the preparation in a small flask.

The study of the "inclusion bodies" which we have described may lead to better methods of investigation of the etiology of this devastating disease.

Subacute lupus erythematosus disseminatus usually produces negative results in sternal marrow tests but in a definite percentage of the cases there may be positive results with the blood serum test.

We express here our thanks to Dr. M. M. Hargraves, who generously took two of us (S. S. B. and T. W. M.) into his laboratories and gave us a week's training in the technic and recognition of the L. E. phenomenon, and to many colleagues all over the country who sent us specimens of lupus erythematosus and control serum.

ABSTRACT OF DISCUSSION

DR. EARL W. NETHERTON, Cleveland: Dr. Lane and associates have given a stimulating discussion of the L. E. phenomenon. This phenomenon is one of the important and intriguing discoveries of modern medicine.

Hargraves, Richmond and Morton were the first to recognize the L. E. cell, which observation led to the discovery of the L. E. phenomenon. The number of important contributions which have been made during the short period of 2½ years since the discovery of the L. E. cell is ample evidence of the significance of these discoveries. I am sure you join me in a feeling of pride that much of what is known about the L. E. phenomenon has come from the investigations of dermatologists. I refer particularly to the present presentation.

Dr. Lane and his co-workers have proved that anticoagulants are not responsible for the production of the L. E. phenomenon in vitro. Their well controlled study has confirmed the observations of previous investigators and justifies the conclusion that the L. E. test is specific for the diagnosis of acute lupus erythematosus and at times shows positive reactions in the subacute stage or period of remission of this disease. This test is of special value in recognition of acute lupus erythematosus without cutaneous manifestations, a type of this disease which is being recognized more frequently now than in the past. The L. E. tests suggest that acute lupus erythematosus is a specific disease entity apart from the so-called collagen diseases.

The production of the L. E. phenomenon in vitro, or the plasma L. E. test, depends on at least two conditions: the concentration of normal mature polymorphonuclear neutrophils, cellular and nuclear debris and the presence of an unknown substance which Haserick, Lewis and Bortz designated the L. E. factor. This factor has been found only in combination with the gamma globulin of blood serum and the plasma of patients ill with acute and subacute lupus erythematosus.

Discovery of the nature of the L. E. factor, its mechanism of production and its immunologic properties may give important leads to the solution of the cause of acute lupus erythematosus. Agitation of the mixture of leukocytes and blood plasma containing the L. E. factor, the amount of L. E. factor present, the prevailing temperature and the length of time elapsing before smears for interpretation are made are additional factors which apparently influence the results of the plasma L. E. test.

The authors have simplified the technic of the plasma L. E. test by substituting the buffy coat layer of normal blood for heparinized normal human or dog bone marrow. This is a distinct contribution for it removes a technical difficulty. Haserick has confirmed their observations and has found this technic satisfactory.

However, he feels that bone marrow preparations show the L. E. phenomenon more clearly and are easier to interpret. Perhaps more experience with the technic just described will alter his opinion.

Further simplification of the plasma L. E. test is desirable and may be possible. A more satisfactory technic would be one eliminating the necessity of using heparinized bone marrow, the buffy coat layer of normal blood or any substance not obtained from the patient ill with acute lupus erythematosus.

That this simplification may be possible was suggested by an interpretation of the observations of Sundberg and Lick, who reported the finding of the L. E. cell in the blood in acute disseminated lupus erythematosus. In view of our present knowledge it seems logical to suspect that L. E. cells observed by Sundberg and Lick were produced in vitro and were not L. E. cells prevailing in circulating blood. The prevailing leukopenia and circulation of the blood prevent the conditions which seem to favor the induction of the L. E. phenomenon in the peripheral blood.

No doubt there are other factors. It is reasonable to suspect that when the L. E. factor of a person ill with acute lupus erythematosus is mixed with a concentrate of the patient's normal leukocytes, rosette formation and development of the L. E. cell should occur.

On the basis of this assumption the following modification of Sundberg and Lick's technic was investigated. To the buffy coat layer of heparinized venous blood from the patient ill with acute lupus erythematosus is added 1 cm. of blood plasma from the same patient. This mixture is placed in a paraffin tube, shaken and allowed to stand for ½ hour. The mixture is then placed in a Wintrobe hematocrit tube and centrifuged. A smear of the buffy coat layer is made and stained with Wright stain. This modified technic has the advantage of intensifying the exposure of the patient's polymorphonuclear neutrophils to his L. E. factor.

Recently we observed positive reactions with this technic in three cases of acute lupus erythematosus. In one case cutaneous manifestations were absent. This technic will be investigated further. The plasma L. E. test should be evaluated by use of a battery of tests.

The report of new intracellular and extracellular bodies is of much interest and deserves further investigation. We have not observed these bodies. Dr. Weiss and his co-workers are to be congratulated on their important contribution.

Dr. Paul A. O'Leary, Rochester, Minn.: The work of Drs. Weiss and Lane and also the work of Drs. Haserick and Netherton has been encouraging to those who have been associated with the development of knowledge of this phenomenon. Dr. Hargraves was conservative in his concept of the "L. E.," cell, and the reports that have been made since his original description not only have been confirmatory but also have materially contributed to developing knowledge of this outstanding observation in disseminated lupus erythematosus. Dr. John Watson, one of my Fellows, and I have developed a technic which materially simplifies the problem of finding the L. E. cell. A cantharides blister up to 1 cm. is produced, and from the blister, by means of curetting of the base a smear is made on a glass slide. The slide is dried rapidly and the material is treated with Wright's stain. It is possible to demonstrate the L. E. cell in all the cases of acute lupus erythematosus in which the bone marrow observations have been positive.

A great variety of control cases have been studied, including examples of all the so-called collagen diseases, and in none of them have we found the L. E. cell. Although the cantharides blister makes for a simple method of demonstrating the L. E. cell, we have not increased our knowledge of the significance of the cell. Dr. Hargraves believes that the cell is a transitional phenomenon of some sort, the exact significance of which is not known at this time.

DR. JOHN T. MADDEN, St. Paul: It should be clearly emphasized that the L. E. cell is only part of the L. E. phenomenon and perhaps the least important part. The L. E. cell is not found in all cases of acute lupus erythematosus. I do not think that anyone has found it in more than 80 per cent of patients, and some have been able to demonstrate the L. E. cell in only half of their patients who had acute lupus erythematosus. Competent hematologists have found the L. E. cell in other diseases, namely, multiple myeloma, leukemia and cirrhosis of the liver. Klemperer, in a paper published in the *Archives of Pathology* (May 1950), stated that bodies similar to L. E. cells were found in the lymph nodes and kidneys in patients with acute lupus erythematosus.

Up to this time the L. E. phenomenon has been considered specific for acute lupus erythematosus. However, it is not always found in acute lupus erythematosus. Haserick had a patient with severe uremia associated with acute lupus erythematosus in which the L. E. phenomenon could not be demonstrated until the uremia was controlled by cortisone. Although the L. E. phenomenon is a most welcome aid in the diagnosis of acute lupus erythematosus, esepcially acute visceral lupus erythematosus without cutaneous manifestations, I think that the subject has not been settled and that further study is needed.

DR. FRANCIS A. ELLIS, Baltimore: My associates and I are working on a paper attempting to differentiate acute and subacute chronic discoid lupus erythematosus on the basis of biopsy observations and were hoping that the authors would give us better clinical or laboratory criteria to differentiate the acute from the subacute stages. In their printed summary we thought that they implied that the L. E. cell was not found in the subacute variety. Since they have found the L. E. cell present in the subacute form, can they give us any criteria for differentiating between the acute and the subacute stages of lupus erythematosus?

McCreight and Montgomery (ARCH. DERMAT. & SYPH. **61**:1 [Jan.] 1950) stated, "Distinction of the type of the disease based entirely on the histologic picture is impossible," but it is our impression that usually the subacute and acute stages can be readily differentiated from the chronic discoid type by the histologic observations and that frequently the acute stage can be differentiated from the subacute stage on this basis alone.

DR. H. E. MICHELSON, Minneapolis: There is no question that the work of Hargraves and others has made the L. E. cell and phenomenon a very important contribution to knowledge of the entire subject of lupus erythematosus. However, I believe one should emphasize that a diagnosis of acute lupus erythematosus can be made in a very high percentage of cases without that observation. This point is important because those physicians who want to make a test for everything would probably question a diagnosis of lupus erythematosus unless this observation were reported as positive. I saw just such an instance in New York a few weeks ago. A dermatologist diagnosed a case as acute lupus erythematosus, and the picture was classic. It was necessary to transfer the patient to the medical service for a trial of cortisone therapy. The internist made the note that the patient showed some signs of lupus erythematosus and that if the Hargraves cell could be found he would accept the diagnosis. Therein lies the danger of depending on a test for a diagnosis which is reasonably simple for one trained in seeing this disease.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: In testing patients with disseminated lupus erythematosus by studying the bone marrow or the plasma according to Haserick's technic, we may not always find the typical L. E. cells. Sometimes these are found in large numbers, and sometimes only an occasional one is found

after long search. The experienced observer appreciates the significance of clumping of cells or the presence of amorphous material even in the absence of phagocytosis. In the present state of our knowledge we are not justified in drawing conclusions as to prognosis from the intensity of the reaction that occurs in vitro, for there are variations not always associated with the degree of intensity of the disease.

DR. RICHARD S. WEISS, St. Louis: We want to thank everyone for the generous discussion and constructive criticism, and we especially are grateful to Dr. Hargraves, who took two of us into his laboratory, showed us everything he had in regard to the phenomenon and trained us in the recognition of every detail in the test as he described it. We also want to thank the men all over the country who sent us blood specimens so that we were able to make the test in quite a large number of cases, some of which could not be commented on in the formal paper.

Since our paper was completed we have had the opportunity to study 10 more patients with acute disseminated lupus erythematosus. Bone marrows of four of these gave positive reactions; six were not examined.

Serums from all 10 were tested against normal leukocytes, and all 10 gave positive reactions to the Barnes-Moffatt test. Six more patients with subacute lupus erythematosus disseminatus were studied. The bone marrow was examined in one of these, and it was positive for the L. E. phenomenon; when the serum of this patient was subjected to the Barnes-Moffatt test it too gave a positive result. The Barnes-Moffatt test result was negative in the five other cases of subacute disseminated lupus erythematosus.

Serum specimens from one more case of chronic discoid lupus erythematosus, one of dermatomyositis, one of acrosclerosis, one of hydroa aestivale and one of ectodermosis pluriorificialis all gave negative reactions.

Four serum specimens from patients with epilepsy who were on treatment with mesantoin® (3-methyl-5,5-phenylethylhydantoin) treatment gave negative reactions to the Barnes-Moffatt test. Testing of these specimens was done as a control because one of our cases of disseminated lupus erythematosus occurred in a patient with epilepsy who had been taking mesantoin® for some months. In 6 more cases of undiagnosed eruptions and fevers the serum gave negative reactions to the Barnes-Moffatt test, and in three of these there was also a negative sternal marrow reaction.

I had the opportunity to read the manuscript of a paper by L. Berman, A. R. Axelrod, H. L. Goodman and R. E. McCloughry, entitled "Morphologic and Serologic Studies of the So-called 'Lupus Erythematosus Inclusion Phenomenon' of Bone Marrow and Blood." The impression was prevalent among some of our men who attended the meeting at which this paper was read that these investigators had found the L. E. cell in many other diseases besides lupus erythematosus. The facts of the matter are that they found one L. E. cell per 500 neutrophils in one case of pernicious anemia in relapse, in one case of dermatitis herpetiformis, in one case of discoid lupus erythematosus and in one case of chronic disseminated lupus erythematosus. They also found two L. E. cells per 500 neutrophils in one case of probably subacute disseminated lupus erythematosus. Three L. E. cells per 500 neutrophils were found in one case of probable collagen disease, type undetermined.

Now, all these observations were in smears of heparinized centrifuged aspirated sternal marrow. The four cases of acute disseminated lupus erythematosus showed 9, 13, 14 and 56 L. E. cells per 500 neutrophils, again in heparinized sternal marrow.

These authors took one sample of heparinized lupus erythematosus plasma and added it to sternal marrow material from persons with 16 assorted diseases and produced L. E. clusters and L. E. bodies. They did not use normal marrow for this experiment.

I quote their exact words in relation to the observation of L. E. cells in "material from patients free of the disease": "Our experience includes six instances in which L. E. cells were found in patients with diseases unrelated to lupus erythematosus, or in cases in which the diagnosis of lupus erythematosus or related diseases could not be clearly established. From this it might appear that the L. E. cell loses much of its diagnostic significance."

However, by the method which they describe they say, "Although it is not apparently a unique qualitative finding there is a significant quantitative difference between acute L. E. marrow and those from other diseases." They further state that "the observation may be considered to have practical diagnostic importance when it is seen in a ratio of approximately ten or more L. E. cells per 500 neutrophils."

The same investigators have reviewed the reports of others who used in vitro tests and state that "the authors were aware of approximately 50 in vitro tests with plasma from patients with diseases of the collagen disease group, patients with leukopenia of unspecified cause and persons with cirrhosis of the liver or hyperglobulinemia, all with negative results. At present it seems safe to assume that the test is valuable and practically specific."

I have been asked whether or not the test showed any correlation with blood grouping incompatibilities. We made no study of this point because Haserick and Bortz stated that there was no correlation between the induction of L. E. cells and blood group incompatibilities.

We make no claim that our in vitro test is infallible. On the contrary, we think it is quite possible that serum specimens other than those from cases of lupus erythematosus may be found that will produce the L. E. phenomenon. But we do say that with the buffy coat technic all the acute lupus erythematosus serum specimens that we have examined gave a positive reaction and all other disease serum specimens examined gave a negative one. Moreover, 30 per cent of the subacute lupus erythematosus serums examined gave a positive reaction. This observation brings up the question of how one differentiates between acute and subacute lupus erythematosus.

Our patients with acute lupus erythematosus were sick: they had intermittent fever, prostration, arthralgia, serositis, leukopenia, a decidedly elevated sedimentation rate and nephritic symptoms, often with blood in the urine. The skin eruptions were usually profuse and polymorphic, but some of these very sick patients had very little efflorescence.

Our patients with the subacute form of the disease had few or several of these conditions but to a lower degree. They were not prostrated, but they usually had skin eruptions which were definite but not extreme.

We think that the inclusion body which Dr. Lane showed you is unique and probably hitherto not described. It possibly represents the beginning stage of the L. E. body. We are reporting it here so that other workers may be looking for it and studying it.

PEMPHIGUS VULGARIS

A Clinicopathological Study of One Hundred Cases

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IN 1941 Gellis and Glass [1] reported on a survey of 170 patients with pemphigus admitted to Bellevue Hospital from 1911 to 1941. In part they came to the following conclusions:

1. The national origins of patients were Russia, 27.2 per cent; United States, 24.8 per cent; Italy, 8.2 per cent, and Austria, 8.2 per cent.

2. The racial stock of patients was Jewish, 49 per cent; Italian, 11 per cent; Negro, 7 per cent, and English-speaking races, 6 per cent.

3. The trunk was the most frequent site of the initial lesion, with the mouth a close second.

4. Analysis of necropsies performed on nine patients showed pathological changes in the adrenal glands in three. The liver in all showed fatty degeneration.

5. No specific treatment routine other than efficient nursing seemed to influence favorably the general course of the disease.

In addition, in 1942 Lever and Talbott [2] presented a clinical analysis and subsequent study of 62 patients admitted to the Massachusetts General Hospital between the years 1921 and 1936.

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 22, 1950.

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, chairman, and the Service of Dermatology and Syphilology of Bellevue Hospital, Dr. Frank C. Combes, chief of service.

1. Gellis, S., and Glass, F.: Pemphigus: A Survey of 170 Patients Admitted to Bellevue Hospital from 1911 to 1941, Arch. Dermat. & Syph. **44**:321 (Sept.) 1941.

2. Lever, W. F., and Talbott, J. H.: Pemphigus: A Clinical Analysis and Follow-Up Study of 62 Patients, Arch. Dermat. & Syph. **46**:348 (Sept.) 1942.

As we at Bellevue Hospital have an unusual opportunity to study pemphigus, we considered it in a sense an obligation to bring our observations up to date. We have reviewed the histories of 100 patients admitted in the last 10 years who remained with us long enough to make our observations of clinical significance. Included, in addition, are accounts of our experiences with treatment with the newer antibiotics and steroid hormones.

Medical science advances not so much as a result of original research and observation of facts as by coordination of those facts. Reviews and the impersonal portrayal of observations regarding a specific disease are often fruitful in stimulating some new ideas on pathogenesis and therapy. We hope our review may indirectly contribute something to the knowledge of pemphigus.

The period of observation of our patients varied from a few weeks to 11 years. In several instances the patient had several hospitalizations.

TABLE 1.—*Diagnosis in One Hundred Cases of Pemphigus*

	Total No. of Cases: 100 Sex: Male..... 49 Female..... 51		
Diagnosis	**Total**	**Women**	**Men**
Pemphigus vulgaris.....	82	45	37
Pemphigus vegetans.....	7	3	4
Pemphigus foliaceus.....	9	3	6
Pemphigus erythematosus.....	2	0	2

Data on the clinical diagnosis and sex of the patients are presented in table 1. It is worthy of mention that the diagnoses presented were those for the majority of the lesions and that often a patient would show typical bullae of pemphigus vulgaris on the trunk and lesions of pemphigus vegetans in the groins and armpits.

A study of the clinical course shows that in many instances the disease started with bullous lesions suggestive of pemphigus vulgaris and, later, in a few weeks or months, the lesions resembled those seen in pemphigus foliaceus or vegetans, only to revert in a short time to the original bullous eruption. The same changes were observed in cases of pemphigus erythematosus, which for months or years preceded the typical lesions of pemphigus vulgaris. We feel that the last-mentioned variety bears the same relation to pemphigus vulgaris as do the vegetative and exfoliative types, with the exception that it precedes it.

The division of our cases according to sex and age is presented in table 2. There was little difference in incidence in the sexes, and the disease occurred mainly between the ages of 40 and 80.

The racial stock of the patients is given in table 3. It shows that 68 of 100 patients were Jewish. The percentage of Italians was 16. It

is worthy of mention that pemphigus foliaceus was, in proportion, more frequent in Negroes.

TABLE 2.—*Age and Sex of Patients with Pemphigus*

Age	Male	Female
20-30	0	1
30-34	0	0
35-39	0	2
40-44	4	4
45-49	4	6
50-54	14	12
55-59	7	4
60-64	4	7
65-69	8	4
70-74	4	8
75-79	2	1
80-84	2	2
85+	0	0

TABLE 3.—*Racial Stock of One Hundred Patients with Pemphigus*

Origin	Total	Pemphigus Vulgaris	Pemphigus Vegetans	Pemphigus Foliaceus	Pemphigus Erythematosus
Jewish	68	59	3	4	2
Italian	16	13	2	1	0
Negro	8	4	0	4	0
English-speaking	7	5	2	0	0
Syrian	1	1	0	0	0
Total	100	82	7	9	2

TABLE 4.—*Places of Birth of One Hundred Patients with Pemphigus*

Place of Birth	No. of Patients
Russia	28
United States	23
Italy	9
Austria	8
Poland	6
Hungary	3
Romania	3
West Indies	2
Lithuania	2
Germany	2
Unknown (not recorded)	14

A study of birthplaces presented in table 4 shows, out of 86 patients, 28 born in Russia and 23 in the United States. Italy, Austria, Poland, Hungary and Romania followed in decreasing numbers. Eight of 23 patients born in the United States of America were of Jewish origin.

The occupation of the patients shed little light on the etiology. The majority of the women were housewives. In men the occupation was

usually one not requiring great strength or effort, as only three patients were laborers; the remainder were salesmen, clerks, musicians, doormen and the like. Many were unemployed, and a few, retired.

Fifty-six cases terminated in death. Data on the duration of the disease, from the appearance of the first lesions to termination, are presented in table 5. The average duration was 9.5 months. The

TABLE 5.—*Duration of Illness to Death in Cases of Pemphigus with Fatal Termination*

Length of Illness	No. of Cases
Less than 1 month	2
1 to 2 months	3
2 to 3 months	6
3 to 4 months	5
4 to 5 months	7
5 to 6 months	6
6 to 9 months	15
9 to 12 months	3
12 to 18 months	4
18 to 24 months	1
24 to 36 months	3
36 to 48 months	1
Total average, 9.5 months	

TABLE 6.—*Sites of First Lesions in One Hundred Cases of Pemphigus*

Sites of First Lesions	No. of Cases
Head	
Scalp	10
Buccal mucosa	36
Nasal mucosa	2
Neck	4
Trunk	
Abdomen and chest	10
Axillas	2
Back	8
Extremities	
Lower	4
Upper	6
Unknown	18

majority (44) of these patients died within nine months, although 12 lived for three, four or more years after the onset of the disease. These observations should not be considered as a true index of the total duration of the disease, as in some exceptional cases it may last many years. One patient has been under observation for 11 years. Incidentally, one patient, not included in this group, has had the disease for 22 years.

SITES OF THE INITIAL LESIONS

In 82 patients the site of the initial lesion was recorded. Data are presented in table 6. In most instances the first clinical evidence was

on the buccal mucosa (this in contrast to observation in Gellis and Glass's cases). In several cases the buccal lesions appeared after the extraction of teeth. Bullae on the scalp often preceded lesions on other parts of the body. With equal frequency lesions appeared on the abdomen and chest; in women often they appeared on or under the breasts.

The period elapsing between appearance of the first bullae confined to one area and generalization varied considerably. In some patients the eruption remained limited to the mouth, scalp or umbilicus for as long as a year. In others there was early, rapid generalization, so rapid that the patients failed to remember the sites of the initial appearance.

CLINICAL DATA

Pemphigus Vulgaris.—The diagnosis of pemphigus vulgaris was made only after a critical evaluation of the clinical, histopathological, hematological and biochemical picture. All cases about which there was no general agreement were eliminated from the observations here.

Data on the site of the first lesions are given in table 6. It is significant that the onset on the mucosa of the nose and mouth and on the scalp was more frequently observed in this type of the disease. In 74 of 80 patients the mucous membranes were eventually affected. Most of the lesions were on the buccal mucosa, the labiolingual folds and the under surface of the tongue, but in many the palate and pharynx were also affected. In addition to the usual bullous eruption on the glabrous skin, there was involvement of the conjunctiva in two patients. The nasal mucosa was affected in five patients and that of the vagina in five. No case of so-called ocular pemphigus is included in this series, as the position of this entity is still uncertain.

The course of pemphigus vulgaris varied considerably. The terms "acute pemphigus vulgaris" (to be distinguished from "butcher's" pemphigus) and "chronic pemphigus vulgaris" were suggested by Talbott, Lever and Consolazio.[3] We think the terms are well taken and appropriate. In the acute variety they found early development of oral bullae, a rapid fulminating course and high racial susceptibility (80 per cent in Jews). In this type constant and early changes in the acid-base balance of hemic electrolytes are seen.

In the chronic type Talbott, Lever and Consolazio found that the disease progresses slowly, with prolonged asymptomatic periods, and has no characteristic racial predominance. Biochemical studies showed but slight and inconstant variations from normal.

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3. Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies on Patients with Pemphigus, J. Invest. Dermat. **3**:31 (Feb.) 1940.

We attempted to follow these authors' classification but encountered considerable difficulty. It was not uncommon to find cases which fulfilled the requirements of the "acute type" pass uneventfully into long periods of remission and, conversely, those with all the requisites of the "chronic type" in which the patients died within a few months. The severity of the initial attack was also found unreliable as a guide to prognosis. Occasionally a patient considered moribund would recover with or without benefit of medication and enjoy a protracted remission. We believe our old concepts of the toxic bullous dermatoses should be revised.

Pemphigus Foliaceus.—In all cases of the exfoliative type the lesions began with bullae on the glabrous skin; in none did they begin on the mucous membranes, and in only two out of nine was there later development of bullae on the oral mucosa. The criteria for diagnosis of this type were strict. One was that at some time the patient present typical bullae histologically compatible with the diagnosis. This criterion eliminated from our series some eight patients diagnosed as having pemphigus foliaceus in other hospitals but classified by us as having idiopathic exfoliative dermatitis.

The scale formation in the foliaceus type of pemphigus differs considerably from that in the erythrodermas. Shortly after its inception the eruption is generalized. Some of the cases begin with greasy, scaly plaques scattered over the trunk, resembling seborrheic dermatitis. Soon flaccid blebs, which are turbid from the first, develop. These blebs sag, the contents flowing to the dependent part. The fact that there is not enough fluid to make them tense causes the roof to wrinkle. Rupture occurs quickly, the discharge drying into a crust which in turn rapidly separates, leaving a raw, denuded surface. The crust is usually shed by formation of another bulla beneath, which "floats" it off. This process can frequently be observed while the crust is still intact, the bulla showing as a milky ring around it, almost in the act of lifting the crust. The epidermis makes an attempt, usually unsuccessful, to cover these erosions, and immature bullae at times make their appearance on the exfoliated area. The clinical picture, therefore, in a well developed case is one of crusts, flaccid bullae, denudations, scaling and seropurulent undermining rings which lift the epidermis, sometimes causing figurate lesions. In some cases the hair and nails may be shed.

The extreme chronicity of pemphigus foliaceus is well known. Four of our patients were hospitalized for over two years prior to their death.

Pemphigus Vegetans.—Three of the seven cases of pemphigus vegetans began with lesions on the oral mucosa. The vegetating lesions in the groins and armpits were often associated with bullae on the

scalp and trunk. One example of this interchange of type was observed in a woman who in two hospital admissions had extensive vegetative lesions, while in a third she had typical bullae of pemphigus vulgaris, the intertriginous areas being free of lesions.

It is noteworthy that pemphigus vegetans was the type most responsive to medication, especially topical antiseptics and antibiotics. The lesions, however, almost invariably recurred within three or four months of cessation of therapy.

Pemphigus Erythematosus.—Of two patients with pemphigus erythematosus, one after two years manifested typical pemphigus vulgaris and died within six weeks. In the other, the lesions had persisted for over three years to the time of writing, despite all treatment.

Associated Diseases.—As expected, a series of associated diseases were encountered, all apparently unrelated to the pemphigus. Three patients had diabetes; one, pernicious anemia; one, gastric carcinoma; one, psoriasis with arthritis; two, latent syphilis; one, rheumatoid arthritis, and three, hypertensive cardiovascular disease. Six patients acquired bronchopneumonia, which was the cause of death in four. With the exception of the last-mentioned condition the associated diseases were found to have little or no influence on the course of the pemphigus.

Loss of Weight.—One of the outstanding clinical characteristics is loss of weight. It was found most consistently in pemphigus vulgaris. In some cases it was lacking, but it was not unusual to find a weight loss of 60 pounds (27 Kg.) over a period of one to two years. Thirty-eight of the 46 patients who died had lost from 10 to 30 pounds (4.5 to 13 Kg.) in the last three months of life, with an average of 13.5 pounds (6 Kg.). We do not think, however, the loss of weight as a diagnostic feature should receive the emphasis placed on it by some clinicians. Some patients actually gained weight. Weight loss may be due directly to the toxemia or indirectly to difficulty in mastication caused by oral and pharyngeal involvement. Seventy-five per cent of patients presenting severe lesions had lost 15 pounds (7 Kg.) or more, although some in whom the disease went into remission recuperated some weight loss.

Pruritus.—Itching is one of the most difficult subjective symptoms to evaluate. Our studies indicate that it is not uncommon; in fact so many patients complained of pruritus, evidence of which could be seen objectively, that we concluded this symptom is of no value in differentiation of dermatitis herpetiformis.

LABORATORY DATA

All patients when hospitalized had a complete blood count, urinalysis and examination of blood chemistry. An effort was made to have the

following studies done weekly: blood count, urinalysis and determinations of blood proteins, sodium, chlorides, nonprotein nitrogen, icterus index, carbon dioxide–combining power and erythrocyte sedimentation rate.

In general, results of these laboratory examinations were of limited value as an aid in diagnosis. None were specific or pathognomonic. They were a great help in treatment. Histopathological examinations were extremely useful. A separate report on this phase is in preparation by Dr. William Director, dermatopathologist of the Bellevue Unit.

The erythrocyte counts and hemoglobin determinations were usually within normal limits in our patients, but occasionally a simple hypochromic anemia was encountered. The total leukocyte count was frequently elevated and became higher as the patient's condition deteriorated. In some instances a decline in the white cell count 48 hours preceding death, as described by Grace,[4] was observed. The differential rates showed a very definite shift to the left and eosinophilia. While the eosinophil count averaged about 12 per cent, values as high as 35 per cent occurred during the active phase of the disease, decreasing or returning to normal in periods of remission. Eosinophilia is of no value in differentiating pemphigus from dermatitis herpetiformis. In 13 of 46 patients who died there was a fall in the number of eosinophils two or three weeks before death.

The determination of the erythrocytic sedimentation rate is a nonspecific test considered by most clinicians as an index of toxicity. We found it of some value. This observation confirms the study made at Bellevue Hospital by Tulipan and Director.[5] The indicated toxicity paralleled that expressed by the Pels-Macht test, the results of which were extensively commented on by Gellis and Glass. We do not consider this determination of value diagnostically, although it is significant prognostically.

Chemical studies of the blood showed that 85 per cent of the patients had consistently low blood chloride levels, 90 per cent low proteins and 70 per cent low calcium. All levels varied with the clinical course of the disease, the most stable being those for the total proteins. Likewise the last-mentioned were the easiest to control therapeutically. Cholesterol and nonprotein nitrogen values were within normal limits in the majority of cases. Results of liver function tests also were found

4. Grace, A. W.: Pemphigus: Study of Blood Picture, Arch. Dermat. & Syph. **55**:772 (June) 1947.

5. Tulipan, L., and Director, W.: Red Cell Sedimentation Test in Dermatology, Arch. Dermat. & Syph. **27**:759 (May) 1933.

to be usually within normal limits. The McClure-Aldrich test [6] showed a rapid disappearance of the wheal independent of the gravity of the clinical picture. This test may be helpful in differentiation of toxic erythema bullosum. In that disorder the readings return to normal in periods of remission, whereas in pemphigus disappearance of the wheal is rapid even in remission.

TREATMENT

The treatment of pemphigus during the past decade has followed closely the general developments of therapeutics. All new drugs have been hopefully and many times empirically tried, from the sulfonamides to cortisone. Some have afforded temporary improvement, only later, on continued or renewed administration, to fail completely.

As in other diseases featured by spontaneous remissions it is extremely difficult to assess a medicament in pemphigus. Besides, most internal drugs in our series were used simultaneously with topical remedies. Some patients with prolonged periods of hospitalization had as many as 10 so-called specific medications successively, many types of topical therapy and a substantial list of supportive remedies.

One significant fact is that initial improvement followed hospitalization with remarkable regularity, usually before administration of any systemic medication. This subjective and objective improvement was of sufficient importance to justify comment in 45 per cent of patients. In our opinion it was due to good nursing care, bed rest and a nourishing diet. All too often the enthusiastic clinician attributes this initial improvement to some medication. Unfortunately, however, this remission does not persist, for within a few weeks, or months, new lesions appear and then the drug which originally was falsely credited with therapeutic virtues is adjudged valueless. This relapse has a very bad psychic effect on the patient.

That there is no specific treatment is the only conclusion which can be reached after a study of the long list of remedies prescribed. Arsenic, an old medicament for pemphigus, has been found equal and in some instances superior to other more modern and more expensive drugs. In our hands carbarsone gave satisfaction in many cases, and we feel that this drug has materially lengthened the lives of several victims. Some patients are now taking maintenance doses of it while the disease is in remission and have been following their normal pursuits for several years with few or no lesions.

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6. Canizares, O.; Combes, F. C.; Simuangco, S. A., and Kaufman, J. J.: The McClure-Aldrich Test in Dermatology, J. Invest. Dermat. **13**:325 (Dec.) 1949.

LOCAL TREATMENT

Among external therapeutic measures, baths occupy a prominent position. The solution most frequently used was potassium permanganate; but benzalkonium (zephiran®) chloride and alibour water (water containing zinc and copper sulfates) were often found satisfactory. Wet dressings with dilute aluminum acetate (Burow's) solution, chloresium® (containing purified therapeutically active, water-soluble derivatives of chlorophyll "a") and topical applications of methylrosaniline chloride and brilliant green were often used. The latter dyes were not particularly effective because of their tendency to form crusts. Of fatty dressings, chloresium® ointment, desitin® (containing chlorinated cod liver oil, zinc oxide, talc, hydrous wool fat and petrolatum), ultracain® (containing sodium propionate, 2 per cent; amyl paraaminobenzoate, 0.7 per cent; ethyl aminobenzoate, 0.2 per cent, and cod liver oil, 20 per cent, in a partially absorbable lipophilic base) and petrolatum were preferred by most patients. We found an acriflavine-petrolatum mixture one of the most soothing and effective preparations. Because of the insolubility of acriflavine hydrochloride in fats and petrolatum the following formula is suggested:

	Parts
Acriflavine hydrochloride	0.1
Glycerin	1.0
Oleic acid	4.0
Ammonium hydroxide solution	2.0
Chloroform	18.0
Petrolatum	to make 100.0

Dissolve 1 Gm. of acriflavine hydrochloride in 10 cc. of glycerin by heat; add 40 cc. of oleic acid and 20 cc. of ammonium hydroxide solution; stir until the mixture is completely liquefied. Allow the mixture to stand until it is viscous, and then put it into a dry bottle containing 180 cc. of chloroform; shake well to complete solution, and pour the preparation into previously sterilized heated petrolatum in sufficient quantity to make 1,000 cc.

Acriflavine hydrochloride, 1 per cent in 50 per cent alcohol, is useful, dabbed on lesions with a cotton swab.

SYSTEMIC TREATMENT

Systemic treatment may be divided into two categories: supportive therapy and specific therapy. In the former, the methods and substances most commonly used were crude liver extract, hydrochloric acid, vitamins, protein hydrolysates, ferrous sulfate, autohemotherapy and typhoid vaccine.

Among the so-called specific drugs those used most frequently were moccasin and cobra venoms, bismuth arsphenamine sulfonate (bismarsen®), stibophen (fuadin®), carbarsone, protamide® (a stable, sterile, colloidal solution of processed and denatured proteolytic enzyme for intramuscular injection), suramin sodium, desoxycorticosterone, diphenhydramine hydrochloride, the sulfonamides, penicillin, streptomycin, aureomycin, chloramphenicol, terramycin, adrenocorticotropic hormone

and cortisone. Those which were given to a sufficient number of patients to permit evaluation will be briefly considered.

Desoxycorticosterone Acetate (Cortate, Doca®).—Six patients received cortate for periods varying from three weeks to four months. There was some improvement in three, but the rest failed to show any response. The simultaneous administration of ascorbic acid in doses up to 1,000 mg. daily likewise contributed nothing. We feel, however, that this adrenal steroid hormone has definite value on occasions in pemphigus.

Carbarsone.—Carbarsone is a reduction product of arsonic acid, containing about 28.5 per cent of pentavalent arsenic. Fifteen patients were given it; eight showed startling improvement, but seven were not apparently helped. Of the eight whose condition improved, four are still alive and with the disease in remission. One has been taking carbarsone with but brief rest periods for over 10 years. The dose given our patients was begun at one 250 mg. tablet taken daily by mouth before breakfast for one week; subsequently, each week, an increase of 250 mg. was made until a total daily dose of 1 Gm. was reached. The drug is usually well tolerated, especially if sodium paraaminobenzoate is given every two or three hours in doses of 100 mg.

Suramin Sodium (Naphuride® Sodium, Bayer 205, "Germanin").—Suramin sodium is a carbamide, originally employed as a trypanosomicide, intravenously or intramuscularly. In our hands it failed to cause any improvement. Eight patients received 500 mg. for from four to six doses. In all instances the disease pursued its course unaffected. Three patients showed evidences of serious renal irritation.

Penicillin.—Twenty-one patients received penicillin. When this antibiotic was a novelty it was given with great expectation and hope, but it was soon evident that it affected only secondary infection. With this point in mind, therefore, penicillin was used for the treatment of intercurrent diseases such as pneumonia. Doses varied up to 1,000,000 units daily.

Aureomycin and Chloramphenicol (Chloromycetin®).—Aureomycin and chloramphenicol were given to 12 patients. In one case of pemphigus vegetans the condition improved rapidly but relapsed and then failed to respond on readministration. Four had temporary remissions, and in seven the disease followed its course unaffected. The nausea caused by aureomycin was a serious inconvenience, and in several instances for this reason treatment with this antibiotic had to be discontinued. The average dose was 250 mg., four to six times daily. With aureomycin intravenous and rectal routes were sometimes used. We feel that these two antibiotics, like penicillin, have some effect on secondary infection and not, as has been suggested, on a causative virus.

Terramycin.—Other than for some effect on secondary infection, which was not startling, terramycin failed to be of any benefit.

Cortisone.—Cortisone is being used currently on several patients, and, while we are hopeful, it is too early to evaluate the drug accurately. Six patients have received it; one died, and two showed no improvement although one of these gained weight and enjoyed a brief period of euphoria. The other, a woman with pemphigus vulgaris, acquired, within a week, typical pemphigus foliaceus which had persisted at the time of writing for two months. She became depressed and morose during the administration of cortisone and improved mentally on discontinuance of that treatment. One male patient failed to improve and acquired decubital gangrene in the sacral region, an unusual complication in pemphigus.

Two patients enjoyed complete and dramatic remissions and were in the third month of health, under small maintenance doses, at the time of writing. In all cases the number of eosinophils decreased rapidly.

Pituitary Adrenocorticotropic Hormone (ACTH).—One patient received ACTH for three days without benefit. Since it has been observed that patients with pemphigus who became jaundiced simultaneously had improvement in their condition, it is hoped that there is a common denominator between the disorder and adrenocortical function. It is not beyond reason that, although we are striving to cure the disease by means of antiseptics and antibiotics, its course may be profoundly influenced by remedies whose action is primarily biochemical.

SUMMARY AND CONCLUSIONS

One hundred cases of pemphigus are reviewed, consisting of 82 of pemphigus vulgaris, 7 of pemphigus vegetans, 9 of pemphigus foliaceus and 2 of pemphigus erythematosus.

The racial incidence was Jewish, 68 per cent; Italian, 16 per cent; Negro, 8 per cent; English speaking, 7 per cent, and Syrian, 1 per cent.

The initial lesions appeared most frequently in the mouth; the scalp, abdomen and chest, in that order, had the next most frequent involvement.

Blood counts, sedimentation rate determinations, studies of blood chemistry, the histopathologic picture and the McClure-Aldrich test were found to be of some value in diagnosis.

A highly nutritive diet and good nursing care are essential.

There is no specific treatment. With carbarsone as good results were obtained as with the antibiotics. The latter substances probably act only in controlling secondary infection. Cortisone deserves further evaluation.

ABSTRACT OF DISCUSSION

DR. ASHTON WELSH, Cincinnati: I was interested in this statistical study of 100 cases of pemphigus by Dr. Combes and his collaborators because clinico-pathological surveys of this type not only serve to clarify existing conflicting clinical views but also in many instances stimulate new ideas on pathogenesis and eventually on therapy.

In general, the observations regarding nationality of the patients, racial status, distribution of disease types, age and sex incidence and occupational background in the present series all correspond favorably with previous statistical reports of large groups, such as those of Gellis and Glass, Lever and Talbott and Eller and Kest.

Their observation that only 56 per cent of their patients with pemphigus died of the disease confirms the expressed opinion of many dermatologists that this disease is not uniformly fatal and is consistent with the data which I reported in connection with discussion of a serologic test for this disease in *The Journal of Investigative Dermatology* for July 1948.

I was somewhat surprised to note the high incidence of location of the initial lesion in the mouth in this series. The percentage of patients who eventually acquired mucous membrane lesions during the course of the disease was also high in comparison with that noted in earlier reports. Dr. Combes and associates pointed out that the severity of the early course of the disease could not be used prognostically.

The concept that loss of weight is a diagnostic feature of pemphigus or is a criterion for unfavorable prognosis did not hold in this series, and that observation is worthy of comment. The observation that the presence or absence of pruritus could not be used diagnostically or prognostically is, I believe, in agreement with the opinion of most of us.

The presenters pointed out that eosinophilia was common, fluctuating with the course of the disease, and consequently could not be used to differentiate pemphigus and dermatitis herpetiformis. This point regarding eosinophilia has been borne out in recent reports. In Dr. Combes and co-workers' series, as in others already reported, differential rates showed a pronounced shift to the left.

The presenters found that the sedimenation rate varied inversely with the poor status of the patients. It obviously measured toxicity and might be of some significance prognostically but certainly not diagnostically. They expressed the same opinion regarding the Pels-Macht test. I was somewhat disappointed to note that they did not include the Macht-Ostro test results for these patients. I feel that both of these tests simply measure toxicity.

The results of blood chemistry studies reported in this paper are consistent with those reported by many authors and reveal evidence of regular changes in the acid-base balance in persons with pemphigus. It would have been of great interest to me had the authors elaborated on these acid-base studies, since it is my opinion that a decided advantage in supportive therapy may result from such studies. Their observations with the McClure-Aldrich test were consistent with those reported by various authors and demonstrate further evidence of the acid-base imbalance in persons with pemphigus. There are many pitfalls in the interpretation of this test, and it is my opinion that repeated tests should be done before an interpretation is expressed.

The authors' summary of therapeutic approaches confirms the reported opinions, first, that the antibiotics simply control secondary infection but do not otherwise influence the course of the disease; second, that arsenic, particularly carbarsone, has a definite favorable effect on patients with pemphigus—the Davis

and Davis procedure in our hands has been equally effective; third, that cortate is without effect in many patients with pemphigus, this observation differing sharply from the conclusions stated in the report of Lever and Talbott, and, fourth, that to date there is no specific or satisfactory therapy for this disease.

The authors' report on the use of cortisone and adrenocorticotropin (ACTH) in patients who had pemphigus is of decided interest. On investigation, I found it is agreed by the few men who have used them that these agents have a definite corrective action on the disturbed acid-base and water balance.

Apparently these agents have a temporary, favorable effect which may permit the use of other agents which otherwise would not have time to act in a severely ill patient, and, in this sense, they may be of value in the management of this disease. However, it appears that in the small number of cases treated no effect was manifest on the underlying cause of the disease as a result of their use.

I was disappointed that the autopsy reports on the 56 patients who died were not included, particularly that the observations with regard to the adrenal glands (which have raised such controversy) as well as the other glands of internal secretion were not recorded. Confirmation or refutation of the observations of Goldzieher and of Lever and Talbott might have been revealed.

It is my hope that the authors will favor us with a subsequent report including histological data and more extensive laboratory observations, particularly on the blood proteins and electrolytes, since then, from a series of this magnitude, some contribution might be made to knowledge of the etiology and pathogenesis of the disease.

Dr. George C. Andrews, New York: Dr. Combes and Dr. Costello have vast experience in work with pemphigus at Bellevue Hospital in New York, and they selected 100 cases carefully from their liberal material and reported on them. This paper is a very important one, not clinically but with regard to therapy. I disagree a little bit with Dr. Combes that aureomycin and some of the other antibiotics simply control secondary infection. I don't think one can pass by their effect quite as easily as that.

The same thing occurs with arsenic in some cases. The same thing also happens with cortisone and ACTH in some cases. The blisters just stop coming and disappear, and the condition gets better for a time. I don't think the reason is just control of secondary infection. The pemphigus is apparently ameliorated. The course of it is modified by large doses of aureomycin for a long time, and then later the patients succumb to the disease.

As far as ACTH and cortisone go it seems that they are like insulin. They have to be given continually. The maintenance dose is felt to be different for different persons and has to be increased up to a point where the treatment does not work any more. My associates' and my figures are very much like those of Dr. Combes'. We treated approximately the same number of patients, with one death and two apparent cures. People have been moribund and have recovered and don't have any more bullae except one or two occasional ones in one area. They go back to work. The disease doesn't trouble them.

One of the outstanding effects of cortisone and ACTH is the sense of well-being the patients have. Within a few hours after the first dose a moribund person will feel better and want something to eat. We had one man eating three meals three times a day. He would have three breakfasts, three lunches and three dinners; he got back his strength and went back to work; we kept him on a maintenance dose, and then he got sick again.

ACTH and cortisone will stimulate our interest in the chemical study of the disease and in hormones in general. They are disappointing because they are

temporary uplifters. They give temporary improvement, and I think in the long run we are going to be rather let down by cortisone and ACTH unless they can be made inexpensive, because they do not cure many people. They cure a very few. They help temporarily. One has to keep on endlessly giving treatment with them. In closing, I should like to ask Dr. Combes whether he in his vast experience has seen any case of essential shrinkage of the conjunctiva (so-called ocular pemphigus) develop into pemphigus vulagris.

Dr. Samuel Ayres Jr., Los Angeles: Dr. Combes' series is an extensive one. I have not had the opportunity of seeing as large a number of cases of pemphigus as that. But over the years I can credit at least six of what I consider cures in typical pemphigus vulgaris, although I will admit the diagnoses were not confirmed histologically. The cases were running the usual course and were accepted as being pemphigus by other competent dermatologists. My conception of pemphigus has always been that it represents a bacterial allergy. I think that is not a new idea. Dr. Welsh has emphasized that point.

But, if one accepts the thought that pemphigus is one of the manifestations of bacterial allergy, then, if the source of the allergy is not removed, the patient is not going to get well regardless of whether he is given antibiotics, sulfonamides or what have you. There can be a variety of manifestations of bacterial allergy. Urticaria is one. In case of chronic urticaria the seat of action is in the cutis. There is no escape of tissue fluids or loss of protein; the edema fluid is merely reabsorbed. In case of pemphigus the seat of action is at a higher level, and there is bleb formation with loss of tissue proteins and all the serious consequences which ensue in such cases.

The clinical effect is exactly the same as in a patient with a severe and extensive burn. It is well known that the patient who has a large part of his body surface burned is not going to survive very long; the toxemia, loss of proteins and other effects of extensive burns are going to cause interference with nutrition, damage to the kidneys and adrenal glands and other injurious effects. I think many of the symptoms we find in pemphigus are due to these secondary effects of the location of the disease process.

The first thing, to my mind, that should be done in a case of pemphigus is to get rid of whatever focus of infection is present, regardless of the stage of the disease. It is always difficult to induce a dentist to remove infected teeth in a case of pemphigus. Nobody wants to touch the patient. And it is equally difficult to persuade a nose and throat specialist to take out infected tonsils.

But the cases in which a cure resulted—and I mean those in which the patients have been cured over a period of years—were handled by administration of, first, sulfonamides and, recently, antibiotics to the point of arresting the process and also by institution of removal of obvious foci of infections. I have never seen a person with pemphigus vulgaris who did not have a most obvious focus of infection. Even though there may be a temporary exacerbation of the disease following removal of the focus, I think that the treatment outlined offers the only chance of saving the patient's life.

Dr. Louis A. Brunsting, Rochester, Minn.: It is an unusual privilege to have the experience of listening to some one who has studied 100 cases of pemphigus. We are still in the dark as to the cause of this disastrous disease. Many patients present bullous reactions for which we consider the diagnosis of pemphigus vulgaris, but I believe we should be careful in using this term in the hearing of the patient when we discuss the diagnostic probabilities, chiefly because of the psychiatric effect of the word pemphigus.

It has been our experience that electrolytic changes in patients with pemphigus are usually a late observation in the disease and are probably secondary to a loss of fluid from the surface of the skin, as well as a depletion otherwise of the protein reserves. The administration of whole blood and plasma is temporarily useful in bringing about temporary remissions, and, moreover, since the introduction of the sulfonamides and antibiotics, the effect of intervening infections can be more or less controlled. We have applied cortisone and ACTH to five patients with pemphigus and allied blistering eruptions and noted that during the administration of quantities of these hormones the symptoms could be suppressed, although the effect was temporary and the long range results were disappointing.

Dr. Earl D. Osborne, Buffalo: I think the occasion should not pass without referring at least a minute to the work of Macht. Some of us at the American Medical Association meeting three years ago in astonishment heard Macht claim remarkable results from the use of irradiation to the blood stream done by exposure of the liver and spleen to a certain quantity and quality of radiation. Macht claimed apparent cure in a series of three or four cases out of about six or seven. I have forgotten the exact percentage, but at least he claimed remarkable results.

He also stated that by means of phytopharmacological methods he was able to demonstrate detoxification of the blood serum of pemphigus patients after the serum had been exposed to radiation. That is, a Macht test made after exposure of the serum to radiation in a test tube did not indicate a toxic serum.

Well, my associates and I were very skeptical of this idea, but we made up our minds we would try the treatment, and in a series of 10 cases we have observed three or four very dramatic results including that in the case of a man 90 years of age with a severe pemphigus that cleared up promptly and remained clear for a period of three years, to the present. We have treated two other patients with very severe pemphigus, with dramatic results. I mention this point because we should not overlook any method of possible value in the treatment of pemphigus.

Dr. C. F. Lehmann, San Antonio, Texas: I had during the war the following experience. A 30 year old man with severe pemphigus was given repeated blood transfusions, using the blood of a patient who had recovered from the Steven-Johnson syndrome. The recovery in this case which looked absolutely hopeless left indelibly in my mind the impression that further investigation should be done with regard to therapeutic developments concerning antibodies in the blood. I wonder whether it would not be a good idea to establish a pool of pemphigus serum and attempt some method to see whether desensitization of stimulation might be possible by use of that therapy.

Dr. Richard S. Weiss, St. Louis: To our relief and perhaps to yours I want to report that in St. Louis pemphigus seems to be disappearing. We have extremely few cases. During the past year I have seen only one case in our group of hospitals. This was in an 18 year old youth and gave us our only experience with the use of ACTH in this disease. We put the patient on treatment with ACTH, and he manifested rapid improvement and got to feeling so good he insisted on going home; he disappeared from observation, and I don't know his subsequent fate. We cannot report any cures in the last few years because the disease seems to be disappearing in our area. I am certainly indebted to Dr. Combes, and I know we all are, for this magnificent report on such a large series of cases.

Dr. Frank C. Combes: I wish to thank Dr. Welsh and all the other discussants. Of course, it would be impossible to answer all the questions, but I shall do the

best I can. With regard to the acid-base problem, it is important; the condition should be watched by means of weekly carbon dioxide absorption capacity determinations on the blood.

Concerning the administration of cortisone, we give cortisone in a dosage of 100 mg. daily in one injection. If there is clinical improvement and a drop in the eosinophil count to normal the dose is reduced as rapidly as possible to a maintenance one of as low as 50 mg., given three times a week. Of course, one must watch out for toxic reactions such as sodium retention and potassium depletion. It is often advisable to put the patient on a sodium-poor diet and give ammonium chloride for the edema.

We do not think the Pels-Macht test is of any value diagnostically. It may be of use prognostically. As I mentioned briefly in my remarks, I think our conception of bullous diseases must be entirely revamped. I doubt that there is such a disease as "pemphigus" which we can unequivocally always distinguish from the toxic bullous dermatoses of other types, including some cases of dermatitis herpetiformis. I think the reason we have such a disease concept ("pemphigus") is that there are differences in immunologic responses and differences in toxicity of various pathogens.

Dr. Andrews asked about the antibiotics. They definitely do have an effect in controlling secondary infection. In some instances they seem to exert some direct effect on the course of the disease. The response is erratic, and I think this may be explained on the basis of sensitivity of the responsible organism to the antibiotic administered. This is never constant. It is important in assaying response to medication to remember that pemphigus is featured by spontaneous remissions. Patients often have spontaneous improvement without benefit of specific medication. Furthermore, there is a definite psychosomatic effect of any medication, especially if the patient knows it is one of the "wonder drugs." Hospitalization, good nursing, a highly nutritive diet and a cheerful mental attitude are often more conducive to improvement than any medication.

I agree entirely with Dr. Ayres' remarks on the pathological resemblance of pemphigus to extensive cutaneous burns. I will add that the treatment of pemphigus should be directed along lines similar to the treatment of burns. Many of the manifestations of toxicity are identical in the two.

Dr. Brunsting asked about prognosis. This is never good, and I have grave doubts that any of the antibiotics do more than defer for a brief time the ultimate fatal outcome of most cases of pemphigus. In this regard we have a prognostic sign suggested by Dr. Kossmann, one of our internists at Bellevue: "When the flies begin to collect on the patient the prognosis is bad." This sign never fails.

I have had no experience with radiotherapy, as mentioned by Dr. Osborne. Undoubtedly pemphigus does place the reticuloendothelial system under severe strain, but I fail to see what benefit would accrue from irradiation of the spleen.

I think that I have covered most of the questions. I wish to thank everyone again for his stimulating discussion.

FORMALDEHYDE IN THE TREATMENT OF WARTS

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SINCE warts do not always respond to the simple and usually effective measures directed against them, further therapeutic experimentation may rightly be attempted, particularly for periungual warts and large or numerous plantar warts or plantar warts persisting after radiotherapy, each of which condition is likely to resist treatment. Dermatological attention was redirected to the use of formaldehyde against plantar warts by Sydney Thomson [1] in 1943, but the drug had been used previously, though its history is not clear. It is mentioned rather casually in foreign general reviews of therapy,[2] and American dermatologists trained abroad have long used it in this country, especially against condylomata acuminata.[3] Caro [4] mentioned it as an old drug but a useful treatment for periungual warts. Thomson's method was the daily soaking of plantar warts in a 3 per cent aqueous solution of formalin. For a time one of us used 3 to 10 per cent solutions of formaldehyde but soon modified the method because of its inconvenience, incorporating formalin (solution of formaldehyde U. S. P. XIII) in aquaphor® (an oxycholesterol-petrolatum ointment base), directing that the preparation be rubbed on the wart once or twice daily.

From the Division of Dermatology, University of Minnesota, Dr. H. E. Michelson, director.

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 22, 1950.

1. Thomson, S.: Treatment of Plantar Warts by Formalin, Brit. J. Dermat. **55**:267 (Nov.) 1943.

2. Schäffer, J.: Therapie der Haut- und venerischen Krankheiten, ed. 6, Berlin, Urban & Schwarzenberg, 1922, p. 148. Siebert, C., in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1934, vol. 1, p. 567.

3. Sweitzer, S. E., and Michelson, H. E.: Personal communication to the authors.

4. Caro, M. R.: Old Dermatologic Drugs Which Should Be Retained, Arch. Dermat. & Syph. **60**:1077 (Dec.) 1949.

Written reports have failed to allow exact conclusions as to the effectiveness of formaldehyde. Thomson reported favorably on treatment of 39 plantar warts, with two failures and six patients lost from observation. Sneddon and Parkin [5] reported eight cures in 12 trials, with youngsters responding better than adults. Other comments have been favorable but brief and thus indefinite.[6] In an attempt at evaluation, we have reviewed records of 736 private patients with warts, seen from 1945 to 1949, of whom 177 were treated with formaldehyde in aquaphor®; a few additional patients were treated with formaldehyde soaks in 1944 as well as in the later period. As in most reviews of private patients the frequency and duration of observation were not ideal. Therefore the series was supplemented by more careful observation of groups of patients from various clinics. Excluded from consideration in this review were warts other than common, palmar, plantar or periungual.

PRIVATE SERIES

Because of multiple lesions the number of warts was much greater than the number of patients: 68 per cent presented 1 to 3 warts; 23 per cent presented 4 to 10 warts, and 9 per cent presented 11 or more warts.

Formaldehyde ointment was used with the following frequency: 1 to 3 warts, 11 per cent; 4 to 10 warts, 46 per cent, and 11 or more warts, 65 per cent.

It is evident that numerous lesions tend to limit the choice of agents which can be applied conveniently or effectively; thus, as the number of lesions increases, the use of formaldehyde becomes relatively more desirable therapy.

A number of patients presented two or more varieties of warts, a total of 771 varieties in the 736 patients, distributed as follows: palmar, 7 per cent; plantar, 29 per cent; periungual, 9 per cent, and common, 56 per cent.

With reference to the type of the warts, the frequency of use of formaldehyde was as follows: palmar, 15 per cent; plantar, 30 per cent; periungual, 62 per cent, and common, 17 per cent.

It is probably general experience that multiple plantar or periungual warts are particularly likely to resist common therapeutic methods, and it is for that reason that we employed formaldehyde more commonly for

5. Sneddon, I. B., and Parkin, T.: Plantar Warts, correspondence, Lancet **1**:424 (March 13) 1948.

6. Russell, B.: Plantar Warts, correspondence, Lancet **1**:303 (Feb. 21) 1948. Livingood, C. S., in discussion on Schildkraut, J. M.: Extensive Verruca Plantaris, Verruca Vulgaris, Arch. Dermat. & Syph. **60**:823 (Nov., pt. 1) 1949. Butterworth, T., in discussion on Schildkraut: ibid.

such cases. A further reason for using formaldehyde was the persistence of lesions after previous treatment by other methods in half the cases in which formaldehyde was later prescribed.

With reference to the results of treatment of the private patients the "estimated results" are based on inadequate frequency and duration of observation in the majority of instances. These figures are recorded chiefly for the purpose of comparison of the various subgroups within the whole survey, while results can be estimated much more accurately in the clinic patients. Results were regarded as "indeterminate" when the patients returned no later than three weeks after starting treatment (even though they might have been improving at that time). They were listed as "failures" if new lesions continued to appear or if old ones enlarged or had failed to improve at the time treatment was stopped or the patient was last seen. "Improvement" was the term applied if the patient was not observed to the termination of treatment but had had steady improvement to the time of his last visit, if his condition was improving at the time of change of treatment (this point is to be elaborated further) or if several methods of treatment were used simultaneously, to different warts, and cure was effected. The term "cure" was applied only in those cases in which all the warts were treated with formaldehyde and had apparently disappeared, with full realization that some of these lesions may have recurred later but the patient failed to return.

Palmar Warts.—There were 6 cases of palmar warts. The results could generally be regarded as "good," but the number of patients treated was small and the detailed figures not significant.

Common Warts.—There were 70 cases of common warts. Improvement was frequent, but cures were few; hence, since other simple therapeutic methods are available, the results must be regarded as unsatisfactory by usual standards. Cures were noted in only 10 per cent and improvement in 33 per cent of the cases.

It was thought that good results might be achieved more easily in treating warts initially rather than after other methods have failed. For this reason, in table 1 the results are listed with classification according to whether or not the patient had received previous treatment, but the differences are such that only the total figures are significant.

It is a matter of opinion as to whether these results are so satisfactory that formaldehyde therapy should be recommended. The "cure" rate for the series is certainly not high, but the cases were selected for treatment by standards unfavorable for achieving a high rate (numerous lesions per patient, many periungual lesions and failure of previous treatment). To us the method seems useful particularly because of its applicability

to cases in which the usually satisfactory methods cannot be applied. As is indicated by the incidence figures in this series, such cases are numerous in private dermatological practice, and additional methods therefore deserve consideration.

In evaluation of the results, the effectiveness of psychotherapy was considered but not regarded as likely to be highly important in cases of plantar or periungual lesions of long duration, previously treated without success, as were almost half the cases. No satisfactory basis for controlled comparison is available with reference to the natural course of warts selected according to similar standards.[7]

TABLE 1.—*Results of Formaldehyde Treatment, Initial and Following Other Measures, of Plantar and Periungual Warts*

	Previous Treatment		
	No (53%)	Yes (47%)	Total
Plantar (63 cases)			
Indeterminate	24%	7%	16%
Failure	15%	23%	19%
Improvement	12%	30%	21%
Cure	48%	40%	44%
	Previous Treatment		
	No (60%)	Yes (40%)	
Periungual (38 cases)			
Indeterminate	22%	20%	21%
Failure	30%	13%	24%
Improvement	26%	53%	37%
Cure	22%	13%	18%

STUDENTS HEALTH SERVICE SERIES

Review of results in the group of 56 students from the Students Health Service, University of Minnesota, throws light on several points. Better results were expected and achieved in this series because of the higher degree of cooperation and the intelligent application of treatment. No severe reactions were observed, and only seven patients (12.5 per cent) noted occasional tenderness or fissures at the treated sites. Cure was achieved in 57 per cent, with no recurrence evident during subsequent observation periods of at least three months in all cases and up to two years in some cases. Another 23 per cent were apparently cured but did not return for adequate observation (total "cured," 80 per cent).

For various and individual reasons the patients were selected for formaldehyde therapy, but the series consisted of a consecutive list of patients to whom this treatment was given. The numbers and types of wart are given in table 2.

7. Pillsbury, D. M.; Zimmerman, M. C., and Baldridge, G. D.: Experimental Controls in Clinical Dermatologic Investigation, J. Invest. Dermat. **14**:359 (May) 1950. (See especially pp. 363-364.)

The results of treatment for the entire student group were as follows:

Patient failed to return	5	12.5%
Failure of treatment	2	
Condition improving when patient last seen	3	7%
Condition improving when treatment changed	1	
Apparent cure (inadequate observation)	13	23%
Cure (observation for 3 to 24 months after cure)	32	57%
Total	56	

When we reviewed the results according to type of wart the following facts became evident.

TABLE 2.—*Numbers and Types of Warts Treated in Students Health Service Series*

	No. of Warts		
	1-3	4-10	11+
Palmar	0	0	1
Plantar	11	5	3
Periungual	14	2	0
Common	3	12	14

TABLE 3.—*Length of Time Necessary for Cure (Fifty Cases)*

	0-4 Wk.	4-6 Wk.	To 3 Mo.	To 4 Mo.	Over 4 Mo.
No.	2	10	26	6	6
Per cent	4	20	52	12	12
Per cent, cumulation	4	24	76	88	100

Palmar Warts.—The single patient with palmar warts had 23 such lesions, and the condition required more than four months for cure.

Plantar Warts.—Cure was achieved in 13 (68 per cent) of 19 patients with plantar warts.

Periungual Warts.—Of 16 persons with periungual lesions 13 (81 per cent) had cures.

Common Warts.—Of 29 persons with common warts 23 (76 per cent) had cures.

Some discouragement results from consideration of the length of time required for cure (in 50 cases in which known), which was longer than that mentioned by Thomson, possibly as a result of our modification of his method of treatment.

The longest period of treatment (more than four months) resulted from the following factors: numerous lesions (23, 10 and 27); multiple deep plantar warts of the heels (two cases) and interrupted and irregular

treatment because of pain in a large wart (1.5 cm.) over an interphalangeal joint (one case).

In this series of students the number of cures was reasonably high, particularly in view of the type and number of lesions resulting from an unfavorable selection. The length of time required for cure was longer than with other therapeutic methods, and that fact probably explains why so many private patients failed to continue their treatment and obtain as good results as the students.

DISPENSARY PATIENTS

In 17 patients from outpatient charity services,[8] the types and numbers of warts, as shown in table 4, were found.

Some additional patients had similar treatment but failed to cooperate, and their cases are not here reviewed. Of the 17 adequately observed cases 13 were subsequently watched for many months without evidence of recurrence. One patient is showing improvement but not a

TABLE 4.—*Types and Numbers of Warts in Dispensary Patients*

	No. of Warts		
	1-3	4-10	11+
Plantar	5	1	2
Common	1	3	4
Periungual	3	0	0

cure as yet. Cure was achieved in the following times (with cumulative figures in parentheses): four to six weeks, 21 per cent; to three months, 53 per cent (74 per cent), and to four months, 26 per cent (100 per cent).

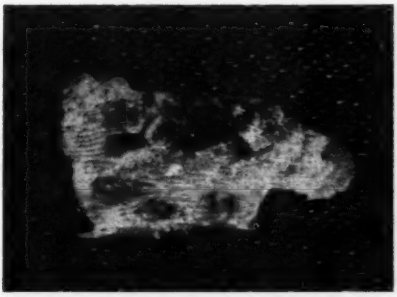
UNFAVORABLE REACTIONS

Probably each reader has wondered as to the unfavorable reactions met with in this series. Without subsequent patch tests it is impossible to estimate how often the treatment produced hypersensitivity to formaldehyde. No patient has returned with contact dermatitis following later reexposure to formaldehyde. Certainly it would seem wise to exclude from this treatment physicians, nurses, laboratory workers, chemists and funeral directors or students in their vocations. However, in these series, from a practical standpoint, the reactions were few and in only several instances were they clearcut examples of contact dermatitis. Generally they consisted in discomfort from cracking and fissuring of warts hardened by the formaldehyde. Such reactions were easily controlled by intelligent patients who regulated the frequency of application

8. From Ancker Hospital and Wilder Clinic, St. Paul.

of the drug. In six of 177 private patients the reaction was such that treatment was discontinued either permanently or for more than a few days. In four additional cases the discomfort was distressing but treatment was soon reinstituted. More frequently the patient left one or two warts untreated for one or two days, applying petrolatum, but continued treatment to his other lesions.

Unfavorable reactions occurred much more frequently in common warts on the thinner skin of the trunk in contrast with that of the hands and feet, and it is our belief that formaldehyde ointment should not be applied to common warts elsewhere than on the hands and feet. Neither do we think the ointment should be applied to condylomas. Such lesions may be painted with solution of formaldehyde, but application of podophyllin (resin of podophyllum N. F.) is preferable.



Occasionally a hard keratotic plug, including much or all of the wart(s), separates or can be trimmed away from the sole.

TECHNIC

The technic of treatment required some judgment on the part of patients as well as physician. A majority of patients were given 15 Gm. of a mixture of 3.0 or 4.0 cc. of formalin in aquaphor.® To some whose warts resisted treatment, and initially to some plantar warts, was applied a similar preparation containing 6.0 cc. of formalin. The ointment was applied with a cotton-tipped applicator and gentle friction and without dressings twice daily for a week or two and then once daily, or once or twice in three days, so that "hardness" of the warts would be maintained. The surface of the lesions was shaved away every week or two, usually by the physician. Rarely was treatment successful in less than four weeks; usually two to three months of treatment was required. Frequently, but not always, the dead warty tissue could be removed *in toto*, as a plug or "cast," as described by Thomson (fig.).

MODE OF ACTION

In spite of biopsies performed during treatment of patients we are in doubt as to the exact manner in which formaldehyde eliminates warts. The separation of a "cast" or easy removal of a "plug" would suggest that the tissue becomes "fixed" as when it is prepared for embedding and the cutting of biopsy sections. This suggestion does not explain why the wart separates from the surrounding tissue, which also takes part in the reaction, becoming dry, firm, and yellow. Perhaps there is selectivity in the effect on the chromosomes, a recognized action of formaldehyde on body cells. The gross and microscopic changes are such as to make it unlikely that the effect is chiefly antiviral.

Biopsy showed pale, amorphous changes throughout the thickened stratum corneum, with many localized areas of focal degeneration. Nuclear changes were noted throughout the stratum granulosum, and retained nuclei were observed in broad areas in the corneum, rather than in the narrower vertical bands often seen in untreated warts. Further study is required before a satisfactory explanation can be offered.

SUMMARY

We believe that formaldehyde in ointment deserves a place in the treatment of warts until more effective measures are developed. Formaldehyde therapy is recommended (1) for large or numerous periungual warts (where electrosurgery or radiotherapy might leave unsightly permanent deformity of nail or periungual tissue) and (2) for palmar and plantar warts (*a*) so numerous as to make radiotherapy too time consuming or (*b*) which have previously received radiotherapy, with contraindication of its further use thereby.

Frequently the treatment was useful even when it failed to cure or was not continued to complete success. Shrinkage in the size of the lesions (especially when periungual) or diminution in their number (especially when plantar) made it possible for us to utilize electrocautery or radiotherapy in some instances in which such treatment would previously have been impractical.

We favor electrosurgery and radiotherapy as generally easier and more frequently successful but regard the application of formaldehyde in ointment as more convenient and effective than cryotherapy, the use of acids and keratolytic therapy. Formaldehyde is suggested not to supplant but only to supplement other therapeutic agents.

ABSTRACT OF DISCUSSION

DR. ANDREW M. DAVIDSON, Vancouver, British Columbia, Canada: In reviewing the results of the use of formaldehyde in the treatment of warts it is to be noted that the results in palmar cases are good but the number of cases is small.

In common warts cures were obtained in only 10 per cent and improvement in only 33 per cent. It is hard to understand why the results should be better in the more difficult types of periungual and plantar cases.

As Dr. Lynch stated, the cure rate is not high, but the ease of applicability and the apparent freedom from reactions observed in this series merit further trial of the method, and search might be made to increase the effectiveness by possibly combining other drugs with the formaldehyde—perhaps podophyllin.

In the students health service series of 56 cases cure was achieved in 57 per cent with follow-up and additional cures were observed in 23 per cent without follow-up. Plantar cures were 68 per cent; periungual, 81 per cent, and common warts, 76 per cent.

However, time for cure was four months, and this fact would appear to negate the value of this treatment for private patients, who quickly grow tired of treatment. Among dispensary patients 13 out of 17 were cured in a four month period. Knowing the potential sensitizing properties of formaldehyde one is impressed with the lack of contact dermatitis in the series.

The authors are to be commended for their caution and judgment in recommending the exclusion from treatment of physicians, nurses, laboratory workers, funeral directors and students in their vocations.

It is disappointing to note, in view of the favorable results obtained in plantar and periungual lesions, that the authors do not recommend the treatment of another troublesome variety, namely, verrucae planae, especially of the face.

Finally, despite the present era with its wonders and potentialities from the experimental use of radioactive substances, cortisone and ACTH, we will have a serious problem in the eradication of the wart and its many varieties.

We have seen dramatic disappearance of all lesions following the treatment of a single lesion, and yet others have resisted all the treatment our resourcefulness could command. We are, therefore, grateful to Drs. Lynch and Karon for reminding us of a simple, clean and comparatively effective drug, namely, formalin incorporated in an ointment.

DR. HERMAN V. ALLINGTON, Oakland, Calif.: Until someone develops a a therapeutic agent which has a specific effect on the wart virus, any effort to find a treatment which will be effective in this very distressing problem is worth while.

However, I should like to call attention to the fact that the results which men such as Bloch have achieved in psychotherapy of warts compare favorably with those which Dr. Lynch has detailed this morning.

If my memory serves me correctly, Bloch (Bloch, B.: Über die Heilung der Warzen durch Suggestion, *Klin. Wchnschr.* **6**:2271 [Nov. 26]; 2320 [Dec. 3] 1927; Allington, Herman V.: Sulpharsphenamine in the Treatment of Warts, ARCH. DERMAT. & SYPH. **29**:687-690 [May] 1934) reported cures in approximately 90 per cent of juvenile plane warts, approximately 45 per cent of common warts and 70 to 90 per cent of plantar warts. The period of observation was about three or four months.

During the time that I was a graduate student I was given the problem of evaluating the use of sulfarsphenamine in the treatment of warts. In my so doing a control series was treated with distilled water. In both the sulfarsphenamine series and the control group there was roughly the same percentage of cures as reported by Bloch. The cure rate in several series of plantar warts treated with roentgen radiation is also comparable.

I think, therefore, that in all the treatments which we apply to warts other than complete destruction we may be doing very little more than one does with

psychotherapy. Or we may be accomplishing little more than nature would accomplish in the same period in developing the natural immunity which I believe is responsible for the cure in the case of spontaneous disappearance of warts, with which we are all familiar.

However, it may be that formalin, salicylic acid and many of the other preparations which we apply locally act as irritants. They may invoke circulatory or other changes which may in time stimulate and enhance the development of natural immunity processes and hasten the cure.

In any case, I think Dr. Lynch and all others working with warts deserve thanks, because these lesions frequently are a most distressing problem.

Dr. Frank C. Combes, New York: I think Dr. Lynch is overly modest when he says that four weeks is a long time to get rid of a wart. He is also overly modest when he thinks his percentages of cure are low. I think they are good and much better than with roentgen rays. In the care of no other cutaneous infection are there so many acceptable methods of treatment. The late Dr. Fred Wise told me of a woman patient whom he treated for over a year with no success, the wart constantly recurring. He finally informed her he could no longer accept a fee for his efforts but that he wished her to continue her visits until he could permanently rid her of the lesion; doing so took him almost another year.

My first experience with formalin and plantar warts was many years ago. I had given instructions to a patient recently recovered from dermatophytosis for the sterilization of his shoes with a blotting paper soaked in formalin. He neglected to aerate the shoes properly. Naturally, the integument of his soles became well fixed, it requiring several weeks and many soap and water soaks to remove the hardened epidermis. Finally his soles were soft and smooth, two old plantar warts and some calluses having completely disappeared. However, I do not recommend the use of formalin in this fashion.

The action of aldehydes on epidermal tissue is not well understood. They do produce some anesthesia, probably due to precipitation of proteins. They are also in varying degrees disinfectants and virucides. Formalin, of course, volatilizes, and the gas liberated, formaldehyde, is quite penetrating. I have often wondered whether the aldehyde might not have some retarding effect on cellular mitosis, similar to that of podophyllin and colchicin. Heptaldehyde, applied simultaneously with methylcholanthrene, seems to inhibit carcinogenesis. However, after the carcinoma has started it is ineffective.

I should like to ask Dr. Lynch whether he has tried any of the phenolic aldehydes such as vanillin, piperonal (heliotropin), salicylic aldehyde and other synthetic volatile oils. They certainly smell better than formaldehyde.

Dr. Francis W. Lynch, St. Paul: I wish to thank the discussants for their kindly comments and for their interest in the problem. As to Dr. Davidson's inquiry as to the apparently better results in the cases which should be harder to treat, I think they were due, at least partly, to the fact that we did not often treat the simpler cases, regarding the method as one which should not generally be applied in common warts, except occasionally when there were warts on the thickened skin of the backs of the hand or the dorsa of the feet. Then we used it and got good results. In small, flat warts there was too great tendency to cause dermatitis.

With reference to Dr. Combes' comments as to the conservatism of my statements, I don't want you to go home thinking that I am enthusiastic about this method of treatment, and I do not want any of you to go home with enthusiasm and then have the disappointment that so often follows trial of new treatment. Use this method cautiously and patiently.

Dr. Combes discussed the method of treatment and the manner in which the lesion responds. Thomson emphasized the frequency with which the wart came off *in toto*. That result has occurred in only a relatively small proportion of our cases. More frequently there was a hardening of the wart which had to be trimmed repeatedly before the entire wart had sloughed off (if we can call the result that). As to the method of action, we performed biopsies on a few of these patients and have not come to a conclusion.

I have not used any of the other aldehydes and cannot discuss their use. The problem Dr. Allington raised was given consideration, as he suggested. It was difficult to obtain a satisfactory series of control patients because we were not using the treatment routinely. We used it only for difficult cases. Perhaps the best statement I can offer as to a control series is that half of the patients whom we treated with formalin had previously been treated by other methods, and, therefore, it is my impression that the warts would not have disappeared spontaneously in the same proportion in these persons as they would in a completely unselected series such as Dr. Allington was dealing with in his study. I thoroughly agree with him that any treatment of warts should be accompanied with a control series, but I do not see how it could have been with our group.

ABNORMALITIES IN THE CHEMICAL COMPOSITION OF THE SKIN SURFACE FILM IN PSORIASIS

STEPHEN ROTHMAN, M.D.
CHICAGO

ANALYSIS of the surface film of the uninvolved skin in psoriasis as compared with that of the skin of normal persons was undertaken on the basis of a working hypothesis which seems to be in accord with all known data on psoriasis.

Psoriasis, on one hand, has features of diseases caused by microorganisms, such as peripheral spread and central healing of the lesions with formation of annular elements and arciform edges. On the other hand, it is a familial disease with irregularly dominant mendelian inheritance.[1] In the present hypothesis it is assumed that it is the susceptibility to the unknown causative organisms which is inherited. The organism is ubiquitous but only those persons who have genetically induced susceptibility will acquire lesions on contact with the organism. Thus psoriasis is not contagious though it is caused by an infective agent. The lesions of psoriasis can be cleared by application of mildly antiseptic agents such as ultraviolet radiation and ammoniated mercury, tar and chrysarobin preparations, but invariably they will soon recur either in the old or in new places. This observation is the reason that the agent is assumed to be ubiquitous.

Also, it has been assumed that differences in susceptibility are due to differences in the composition of the surface of the skin. Should any differences be found, possibly a rational therapy could be worked out either by addition of lacking elements in skin excretions or by neutralization of abnormal products.

From the Section of Dermatology, Department of Medicine, University of Chicago.

Technical assistance was provided by Henrietta Moritz, B.A., M.A., and Thomas Dutcher, B.A.

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 22, 1950.

This work was supported in part by an Institutional Research Grant from the American Cancer Society and in part by a grant from the United States Public Health Service.

1. Hoede, K.: Umwelt und Erblichkeit bei der Entstehung der Schuppenflechte, Würzburg. Abhandl. a. d. Gesamtgeb. d. med. **27**:211-254, 1931.

PROCEDURE

Material was collected by wiping the skin of normal persons and the uninvolved skin of psoriasis patients on the chest and the back with specially prepared ether-soaked and water-soaked cotton pledgets, respectively. The test persons were ambulatory adults. Wipings on the chest were made from the clavicular line to the waist between the anterior axillary lines and on the back from the level of the scapular spines to the level of the third lumbar vertebra between the posterior axillary lines. The average total area wiped was 2,000 sq. cm.

RESULTS

Ether Wipings.—After the wiping the cotton pledgets were thoroughly extracted with a large amount of ether, and the ether solution was filtered. Estimations of the amount of total fat, the acid number, the iodine number and the amounts of cholesterol and cholesterol esters were made.[2] No significant differences were found between the normal and the psoriatic group with regard to the amount of fat and absolute

TABLE 1.—*Chemical Analysis of Skin Surface Fats* *

	Range		Mean and Standard Error	
	Normal Persons	Psoriasis Patients	Normal Persons	Psoriasis Patients
Acid number	49.7-81.6	30.1-79.2	64.9 ± 3.71 (14)	48.7 ± 4.32 (12)
Iodine number	42.5-77.0	18.5-68.5	54.9 ± 3.12 (14)	41.6 ± 4.64 (12)
Ester cholesterol/total cholesterol, %	60-69	35-60	64.8 ± 2.17 (9)	47.0 ± 3.86 (7)

* Figures in parentheses indicate numbers of estimations.

amounts of cholesterol and cholesterol esters. However, as shown in table 1, significantly lower acid and iodine numbers and significantly lower ester-cholesterol quotients were found in the persons with psoriasis. The individual variations of both acid and iodine numbers in both groups were unusually great. It is felt that in spite of the statistical significance of the data obviously more data have to be collected before it can be definitely stated that low acid and iodine numbers are characteristic for the surface fatty film in persons with psoriasis. They certainly are not absolute requirements for the psoriatic constitution, as in single cases relatively high acid and iodine numbers were found.

The situation is, however, different concerning the percentage relation of esterified cholesterol to total cholesterol.[3] Not only is there a

2. Saifer, A., and Kammerer, O. F.: Photometric Determination of Total Cholesterol in Plasma or Serum by a Modified Liebermann-Burchard Reaction, J. Biol. Chem. **164**:657-677, 1946.

3. In this series cholesterol and cholesterol ester estimations were carried out according to the method of Saifer and Kammerer.[2]

highly significant difference but also the ranges in the two groups are distinctly separate.

Water Wipings.—In preliminary experiments the water wipings of 12 normal persons and eight persons with psoriasis were analyzed for total nitrogen, ammonia nitrogen, urea nitrogen, amino acid nitrogen, creatinine nitrogen and uric acid nitrogen. The p_H of the fresh wipings also was taken. The procedure was as reported previously.[4]

Significant differences between normal persons and patients with psoriasis seemed to be present only with regard to the ratio of urea nitrogen to total nitrogen, the quotient being significantly lower in those with psoriasis. Because some doubt emerged as to the accuracy of the routine method of urea estimation by direct nesslerization [5] if applied to this material, these preliminary data were disregarded and in a new series the relative amounts of urea nitrogen and total nitrogen were estimated with use of the method of Krebs and Henseleit.[6] With this method a substantially higher percentage of the total nitrogen was recovered as urea nitrogen than with the routine method.[3]

TABLE 2.—*Quotient of Urea Nitrogen to Total Nitrogen in Water Wipings* *

	Range	Mean and Standard Error
Normal persons	46.9-80.9	64.8 ± 2.45 (16)
Psoriasis patients	27.2-79.0	48.4 ± 5.62 (9)

* Figures in parentheses indicate numbers of estimations.

Analysis with Krebs's method showed considerable individual variations of the quotient, but there was a highly significant difference between the two groups. The quotient of urea nitrogen to total nitrogen was significantly lower in persons with psoriasis than in normal persons (table 2).

COMMENTS

Kooyman [7] demonstrated that keratinization of epidermal cells is associated with esterification of free cholesterol. The preliminary

4. (*a*) Rothman, S.; Smiljanic, A. M., and Murphy, J. C.: The Nitrogenous Material on Normal Human Skin Surface, J. Invest. Dermat. **13**:317-318, 1949. (*b*) Rothman, S., and Sullivan, M. B.: Amino-Acids on the Normal Human Skin Surface, J. Invest. Dermat. **13**:319-321, 1949.

5. Koch, F. C., and Hanke, M. E.: Practical Methods in Biochemistry, ed. 4, Baltimore, Williams & Wilkins Company, 1943, p. 163.

6. Krebs, H., and Henseleit, K.: Untersuchungen über die Harnstoffbildung im Tierkörper, Klin. Wchnschr. **11**:757-759 and 1137-1139, 1932; Ztschr. f. physiol. Chem. **210**:33-66, 1932.

7. Kooyman, D. J.: LXI. Lipids of the Skin: Some Changes in the Lipids of the Epidermis During the Process of Keratinization, Arch. Dermat. & Syph. **25**:444-450 (March) 1932.

data in the present series indicate that in persons with the inherited constitution of psoriasis the keratinization is faulty so far as this esterification process in the cornifying epidermis is less complete in the uninvolved skin of patients with psoriasis than in the skin of normal persons. However, our analyses were made on the surface film and not on the horny layer proper, and therefore our data cannot directly be compared with the data of Kooyman. They can be compared with those of Marchionini and co-workers,[8] who obtained surface lipids from the skin by removing them with chloroform through a glass bell (so-called skin dialysis). In their material these authors found two thirds of the cholesterol esterified, a figure corresponding well to our 65 per cent average value. However, Marchionini, in sharp contrast to our results, did not find any decreased ester values on the uninvolved skin of psoriasis patients with his method.

Since the introduction of the theory by Grütz [9] that psoriasis is associated with anomalies of fat metabolism it has been repeatedly assumed that a systemic deficiency of esterification of cholesterol may play a role in the pathogenesis of psoriasis.[10] However, the evidence for such a systemic metabolic disturbance in which the liver must play an important role cannot be regarded as conclusive. Madden and Barthell,[11] in spite of using a battery of modern liver function tests, could not confirm earlier data on the occurrence of anomalies of liver function in psoriasis.

An entirely different concept arises when on the basis of the presented data it is assumed that in psoriasis the deficiency in ability of esterification is not systemic but is restricted to the epidermis and that this organ debility is an inherited constitutional anomaly. In this light it becomes understandable that occasional therapeutic results may be achieved in psoriasis by the administration of so-called lipotropic substances such as lipocaic,[12] lecithin preparations [13] and desiccated pancreas

8. Marchionini, A.; Manz, E., and Huss, F.: Der Cholesteringehalt der Hautoberschicht bei der Seborrhöe und bei der Psoriasis: Beiträge zur Kenntnis der pathochemischen Hautkonstitution des Status seborrhoicus, Arch. f. Dermat. u. Syph. **176**:613-645, 1938.

9. Grütz, O., and Bürger, M.: Die Psoriasis als Stoffwechselproblem, Klin. Wchnschr. **12**:373-379, 1933; Arch. f. Dermat. u. Syph. **170**:143-150, 1934.

10. Incedayi, C. K., and Ottenstein, B.: Neuere Untersuchungen über die Beziehungen zwischen Psoriasis und Lipoidosen, Acta dermat.-venereol. **21**:674-698, 1940.

11. Madden, J. F., and Barthell, J. H.: Liver Function in Psoriasis: Preliminary Report, J. Invest. Dermat. **9**:125-130, 1947.

12. Walsh, E. N.; Clark, D. E.; Dragstedt, L. R., and Becker, S. W.: Further Observations on the Use of Lipocaic in the Treatment of Psoriasis, J. Invest. Dermat. **4**:59-67, 1941.

13. Gross, P., and Kesten, B. M.: Treatment of Psoriasis with Lipotropic Substances Derived from Foodstuffs, Arch. Dermat. & Syph. **47**:159-174 (Feb.) 1943.

powder.[14] These materials promote fat transport by mobilizing fatty acids [15] and among other effects may promote esterification of cholesterol.

In this connection it may be worth while to mention the work of Ottolenghi-Lodigiani,[16] who found that normally there is a higher ester fraction of cholesterol in the skin than in the blood.

Many more analyses have to be performed before our concept can be accepted as valid. Against its acceptance militate the data of Marchionini,[8] already mentioned, and also data of Incedayi and Ottenstein,[10] who in their analysis of skin tissue found that uninvolved skin in psoriasis contains a much higher portion of cholesterol esterified than does the skin of normal persons.

On the other hand, the histological findings of Madden in uninvolved skin of patients with psoriasis [17] support to some degree the concept that the constitutional anomaly in psoriasis is an anomaly of the skin organ itself.

The relatively low values of urea nitrogen in our water wipings as related to total nitrogen possibly indicate a weakness of arginase activity in the uninvolved skin of psoriatics. There is some reason to believe that urea on the skin surface derives from arginine,[18] which is split by the enzyme arginase into ornithine and urea.

SUMMARY

Ether-soluble material from the surface of the uninvolved skin of persons with psoriasis has a significantly lower acid number and iodine number than has similar material from normal individuals. However, there is some overlapping of the ranges of values obtained; hence not all patients with psoriasis show this abnormality.

The surface fat film of psoriasis patients has a significantly lower ratio of esterified cholesterol to total cholesterol than does the surface fat from normal persons. The ranges of values obtained do not overlap in the two groups. These observations suggest that possibly the psoriatic constitution is associated with a weakened esterifying ability of the epidermis.

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14. Campana, C., and Gualandi, G.: Tentativo di cura della psoriasi volgare con pancreas "per os," Policlinico (sez. prat.) **54**:7-10, 1947.

15. Sinclair, R. G.: Fat Metabolism, Ann. Rev. Biochem. **6**:245-268, 1937. McHenry, E. W., and Patterson, J. M.: Lipotropic Factors, Physiol. Rev. **24**:128-167, 1944.

16. Ottolenghi-Lodigiani, F.: Studi sulla colesterina della cute umana normale e patologica: Nota II. La presenza nella cute umana del fermento esterificante la colesterina; la colesterinesterasi, Gior. ital. dermat. e. sif. **89**:363-373, 1948.

17. Madden, J. F.: Histologic Studies of Uninvolved Skin of Patients with Psoriasis, Arch. Dermat. & Syph. **44**:655-664 (Oct.) 1941.

18. Hier, S. W.; Cornbleet, T., and Bergheim, O.: The Amino-Acids of Human Sweat, J. Biol. Chem. **166**:327-333, 1946. Rothman and Sullivan.[4b]

The ratio of urea nitrogen to total nitrogen in water wipings from the uninvolved skin of persons with psoriasis is lower than that found in normal persons.

ABSTRACT OF DISCUSSION

DR. JOHN L. MADDEN, St. Paul: Dr. Rothman has made an effort to investigate psoriasis by first proposing a hypothesis that the disease is due to a causative organism and that a psoriasis patient inherits a susceptibility to the specific causative agent. This may be accepted, but the reasons for the assumption are not impressive.

If one accepts the hypothesis, then Dr. Rothman's statement that differences in the susceptibility may be due to differences in the chemical composition of the surface of the skin offers a field for investigation. Heretofore similar studies by Pillsbury have not resulted in proofs that the surface constituents which can be demonstrated affect the growth of known microbes to any great extent.

It is difficult to understand how wipings from the surface gather material from a single layer of the skin; therefore, if a certain chemical is obtained one may first ask where it comes from. It may be true that it comes from the surface and therefore from the cornified layer, but the chemical could also come from the hair, the sebaceous glands or the sweat glands or be excreted by the skin from internal sources. One may ask whether the surface is the seat of the pathologic changes in psoriasis. Certainly there is much to support the theory of an origin in the corium which seems to show that the cause is internal or blood borne.

There are so many observations which make an internal or systemic derangement acceptable as the cause of psoriasis that the theory of a purely external infection is hard to believe. Arthritis, nail changes, erythrodermas and lack of contact cases are just a few examples.

In spite of my remarks I do not belittle Dr. Rothman's work. Any research on any part of psoriasis adds either positive or negative evidence which is valuable and can be utilized in further much-needed studies.

DR. STEPHEN ROTHMAN, Chicago: Dr. Madden objects to the presented working hypothesis on the basis that it is hard to imagine how the chemical composition of the surface could influence the take of an infection. He also claims that the presented hypothesis does not account for the association of arthropathia and psoriasis. Finally, he objects to the principle of analysis of skin surface materials on the basis that they derive from heterogenous sources.

I do not believe that these objections are valid. The role of skin surface fats in immunity of the adult scalp to Microsporon audouini infection is an example of the role of the surface film in infections (*J. Invest. Dermat.* **8**:81-98, 1947). Also, there is good reason to believe that selective regional localization of other superficial fungous infections depends on the regional differences in the composition of the skin surface film (*Tr. New York Acad. Sc.* **12**:27-33, 1949). The combination of psoriasis and arthropathia has been interpreted by geneticists as due to the debility of conjugated genes, and this well evidenced interpretation is in accord with the presented view. For the hypothetical invading organism it is entirely irrelevant whether the products on the surface (which, by the way, also impregnate the spaces between the horny lamellas of the stratum corneum) derive from sebaceous glands, sweat glands or horny lamellas. All that counts is the final mixture on the surface, which is either a favorable or an unfavorable culture medium for the organism.

Although the hypothesis presented is in accord with all known facts, it still may be completely wrong. However, this is not the point, because quite a few erroneous hypotheses have led in the past to the discovery of new facts.

CHEILITIS GLANDULARIS: A MANIFESTATION OF EMOTIONAL DISTURBANCE

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AND
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A REVIEW of recent standard textbooks and current literature reveals that there has been no change in thinking regarding cheilitis glandularis (cheilitis glandularis apostematosa) since the classic report of Sutton [1] in the *International Clinics* in 1914, when he brought forth the hypothesis that cheilitis glandularis was a condition caused by a congenital hyperplasia of the mucous glands of the lips and associated mucous surfaces. Concomitant hypertrophy and hyperfunction are associated with inflammation, secondary eczematous changes and, in many cases, infection. A search of the literature, however, revealed a suggestion by Brocq [2] in his "Précis-atlas de pratique dermatologique," 1921, that some inflammatory diseases of the lips are manifestations of nervous instability and reference to association of the condition with hyperfunction of mucous glands of the entire buccal and pharyngeal cavity.

Recent publications on cheilitis glandularis have been almost exclusively in the European literature, and Iordan,[3] giving a hint that gross congenital abnormality is not usual, said, "In cheilitis glandularis there is hypertrophy, sometimes very slight, of the accessory salivary glands." In the footnote discussion of this article in the "1935 Year Book of

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Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 23, 1950.

Material from the Department of Dermatology, University of Colorado School of Medicine, O. S. Philpott, professor, and the private practice of Dr. O. S. Philpott and Dr. A. R. Woodburne.

1. Sutton, R. L.: The Symptomatology and Treatment of Three Common Diseases of the Vermilion Border of the Lips, Internat. Clin. **3**:123, 1914.

2. Brocq, L.: Précis-atlas de pratique dermatologique, Paris, Gaston Doin & Cie, 1921, p. 854.

3. Iordan, A., and Tarabuchin, A.: Über Cheilitis exfoliativa und glandularis, Dermat. Ztschr. **70**:249, 1935.

Dermatology and Syphilology" [4] Wise and Sulzberger stated that "there is little doubt that in some patients a pre-existing and accompanying neuropathy plays a role."

The few above-mentioned references are the only ones we could find which cast any doubt on the congenital anomaly theory of etiology or offered any suggestion of the true cause.

MATERIAL

This discussion is based on the study of three cases which will be reviewed in an effort to disprove the generally accepted theory of the cause of this condition.

CASE 1.—M. B., a tense and emotionally unstable only child of devoted parents, was seen first at the age of 15 with a typical edematous, crusted cheilitis largely of the lower lip. When the crust was removed an edematous mucous surface was seen in which the orifices of mucous glands were dilated; drops of mucus rapidly formed at these orifices. General and laboratory examination showed no abnormality. In accord with the advice of the current literature (1933) radium was used in the hands of an expert radiologist. Therapy was pushed to the point of atrophy and ectasia over a period of three years with no material change in the lips. There were periods during this time when definite improvement seemed to take place, but at the termination of radium therapy no lasting results were obtained. Afterward, many of these dilated follicles were excised with a small skin punch without benefit; later microcoagulation of these orifices on numerous occasions, when eight to 10 dilated orifices were coagulated at each sitting, produced no lasting improvement.

CASE 2.—A timid white girl aged 18 entered Colorado General Hospital on Feb. 17, 1943, with a history of sore, crusted lips of four weeks' duration. This disorder was accompanied with fever, listlessness, loss of appetite and lack of interest in school work. The observations on complete physical and laboratory studies, including blood counts, urinalyses, a chest roentgenogram, and Wassermann, Mantoux and brucellergen skin tests, were all within normal limits. A typhoid agglutination test gave a positive reaction; however, the typhoid organism was never isolated and later typhoid agglutination tests gave negative reactions. One month later cultures from the lips showed diphtheria bacilli (purulent organism). Cultures for fungi were negative on several occasions. Use of diphtheria antitoxin and, later, roentgen ray therapy were ineffective. Many antiseptics, including sulfonamides given systemically and locally and locally administered gramicidin, were used without benefit.

The patient reentered the hospital in July 1944. She was under a mental strain due to the care of her mother, who was dying of cancer, and there was a history of repeated quarrels with her father and sister. A psychiatrist saw the patient on this admission and reported that she was in a state of hysteria. The condition of her lips was not materially changed from that on her previous admission. The use of penicillin locally and systemically was of no benefit. An elimination routine for all possible contact irritants produced no change in the lip condition.

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4. Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1935, p. 71.

The patient was readmitted on Dec. 13, 1944, and a plastic repair of the lip was undertaken. The diseased 1.5 cm. of the anterior portion of the lower lip was removed, and the mucous membrane beyond this area was undercut and brought up to the vermilion border and sutured. Within 10 days the new mucous membrane was in a condition the same as that seen before surgical treatment.

Fig. 1.—Characteristic appearance of the lips of the patient in case 2 from 1943 to the Spring of 1949.

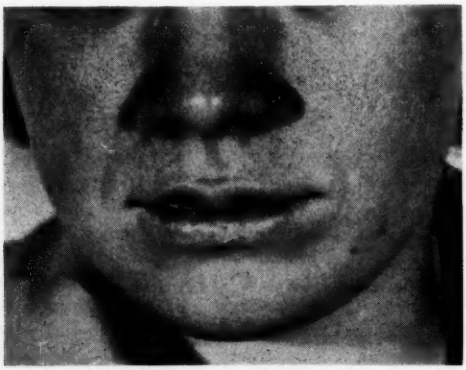

Fig. 2.—Normal appearance of the lips of the patient in case 2 since the Spring of 1949.

The tissue removed at operation was completely studied histopathologically, and the accompanying photomicrographs were taken from this tissue. There was not found any hyperplasia of the mucous glands or evidence of increase in their number or of congenital abnormality. The surface epithelium showed pronounced edema, spongiosis and parakeratosis. The mucous gland ducts were dilated, and there was a diffuse lymphocytic and polymorphonuclear infiltrate in the submucosa. The vessels were dilated, and edema extended deep in the submucosa. In other words, the observations were those seen in eczema and neurodermatitis.

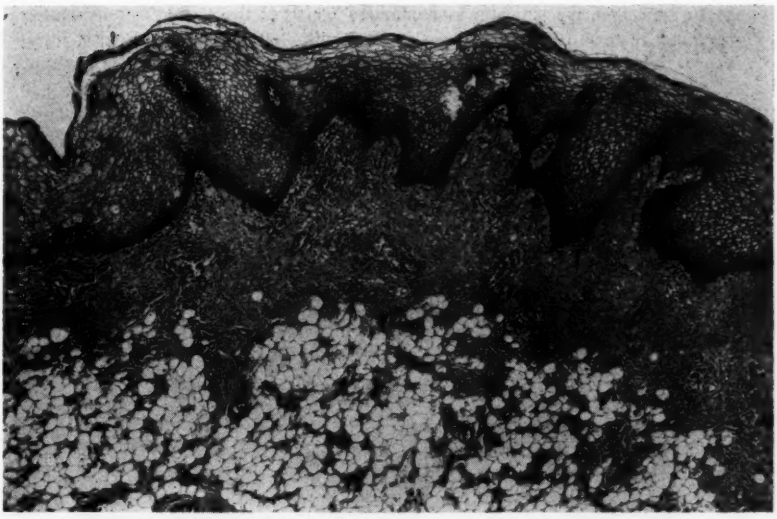

Fig. 3.—Low power view of a section showing changes characteristic of eczema, namely, edema of dermis and epidermis, pronounced intracellular edema, spongiosis, acanthosis and parakeratosis with a diffuse scattering of lymphocytes through the submucosa.

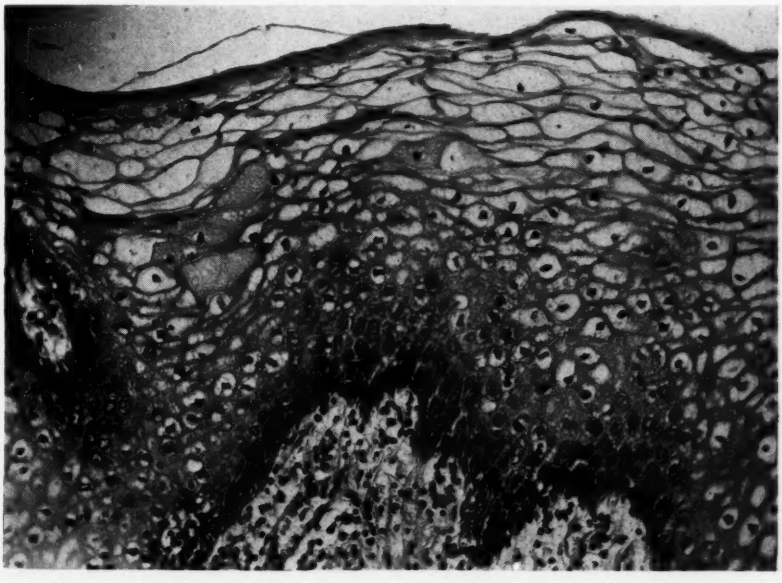

Fig. 4.—High power view showing the pronounced reaction in the epidermis.

In June 1945 the patient was readmitted for fever therapy. Forty-five hours of fever, with a temperature constantly above 100 F., produced with intravenous administration of typhoid and paratyphoid vaccines was given with no effect.

Between admissions various dietary and vitamin regimens were employed without benefit. Cryotherapy with vigorous freezing weekly for five months

Fig. 5.—Low power view showing a normal mucous gland situated deeply in the submucosa.

seemed to produce some benefit, but later there was noted no permanent improvement. With the use of procaine (novocain®), microcoagulation of eight or 10 glands and ducts was done weekly for four months with no material benefit.

At this time, most methods of organic approach having been exhausted and the extremely labile emotional personality of this patient being appreciated, she was turned over to the psychiatric department to see what could be done from their standpoint.

After prolonged study and care in the psychiatric section this patient was seen in the skin clinic with her lips entirely well in April 1949. She was adjudged definitely psychotic and was committed to the Colorado State Hospital for mental patients at Pueblo. A recent letter from her physician there reported that "the cheilitis glandularis with which she had so much trouble before admission has never recurred, and examination of the lips and mouth reveals no abnormality now. Occasionally, when she is somewhat disturbed mentally, a flaky desquama-

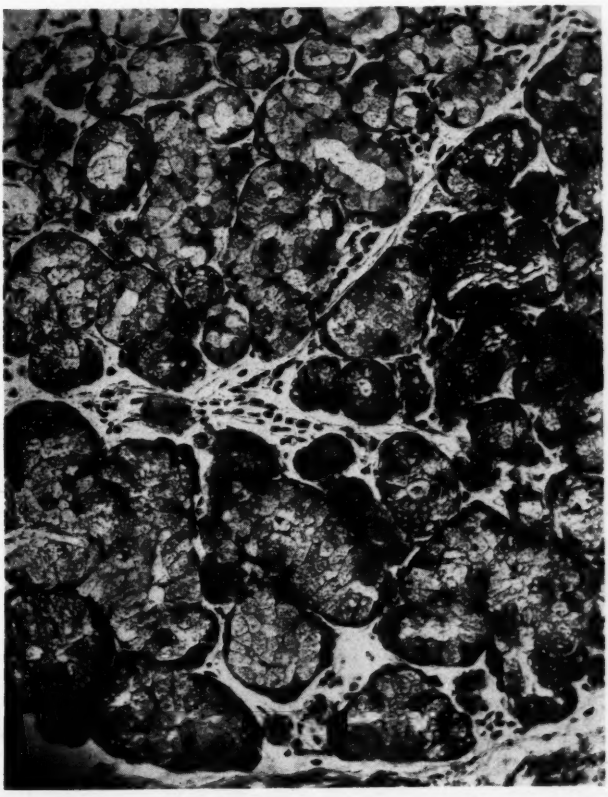

Fig. 6.—High power view of a mucous gland showing an entirely normal gland structure with perhaps slight evidence of hypersecretory activity.

tion of the lips will occur, but this always disappears as soon as she becomes quiet."

Case 3.—A 24 year old male university student had been seen on several occasions in the University Health Service during two years of college work. He had presented no abnormality of the lips. During the middle of his junior year it was necessary for him, in addition to carrying an extremely heavy course in the university, to do much outside work to earn his way. As midterm examina-

tions approached typical dilated mucous gland orifices appeared on his lips, edema of the lips developed and some surface crusting began to form. With the experience with case 2 in mind we put the patient on treatment with small doses of phenobarbital, reassured him in frequent interviews, and had him apply simple local emollients, with pronounced improvement.

COMMENTS

Others [5] reported in cheilitis glandularis a hyperfunction of mucous glands of the entire buccal and pharyngeal mucous membrane.

The analogy between this condition and the syndrome of hyperhidrosis, dyshidrosis and dyshidrotic eczema struck us as being too strikingly parallel to be overlooked. There is much evidence to support the emotional basis of the hyperhidrosis syndrome, and English [6] stated that there is considerable evidence to support this theory of etiological mechanism. MacKenna [7] and Wittkower [8] both wrote supporting this theory. Wittkower found that four fifths of the patients affected with hyperhidrosis and dyshidrosis showed outstanding neurotic symptoms prior to or at the onset of this condition. MacKenna and Wittkower reported that this syndrome is seen in the anxiety states, either evident or hidden. It is our feeling that the ideas expressed by these writers can be directly transferred to apply to the pathogenesis of cheilitis glandularis.

A survey of many sections removed in our case 2 at operation convinced us that there is no congenital abnormality or pronounced hyperplasia of the mucous glands of the buccal mucous membrane or lips in cheilitis glandularis (representative sections are shown in the accompanying photomicrographs). These showed normal mucous glands with some dilatation of gland orifices, parakeratosis and epithelial edema. The mucosal and submucosal infiltrate was nonspecific but closely approximated that seen in eczema and neurodermatitis.

There may be a group of cases of cheilitis glandularis in which a congenital abnormality is responsible; however, we are sure from the study of the above-described three cases that organic causes were not operative in these cases. We feel that we exhausted all organic approaches to this disease and found that we were able to produce no permanent benefit; however, we were able to follow one patient (case 2) for seven years with observations of eventual complete and permanent

5. Sutton.[1] Brocq.[2]

6. English, O. S.: Role of Emotion in Disorders of the Skin, Arch. Dermat. & Syph. **60**:1063 (Dec.) 1949.

7. McKenna, R. M. B.: Psychosomatic Factors in Cutaneous Disease, Lancet **2**:679, 1944.

8. Wittkower, E. D.: The Psychological Aspects of Skin Disease, Bull. Menninger Clin. **11**:148, 1947.

restoration of normal lip mucous membrane by psychiatric therapy. Our other two patients, though not followed for such a long period, gave us additional evidence to support our theory of emotional disturbances as the cause of this condition. In case 2 the patient's exhaustion following the care of her mother during her final months dying of cancer was complicated by her years of conflict with her father and sister. Eventually she was deserted by her family. It was during the development of these complications that cheilitis glandularis developed. The multiple therapeutic methods employed produced no results. Then, in a psychotic episode during which the patient was released from her emotional tension regarding her past desertion by her family and her lack of security, these tensions being resolved in the disassociation of her personality, immediately her lips cleared entirely. With good psychiatric care she has been undergoing a slow readjustment of her personality. She still has periods in which she is disturbed mentally and emotionally upset, during which the lips show some increase in mucous gland activity and superficial desquamation. These periods are of only a few days' duration, and when the patient becomes quiet again the lips return to normal. She wears lipstick most of the time, and the scars of the plastic surgery are evident only on close inspection.

Case 1 illustrates the fact that radiation and other destructive methods can be carried to the point of atrophy and scarring without permanent benefit, while case 3 illustrates the possibility of early control with the proper approach.

SUMMARY

A report of three cases of cheilitis glandularis pointing to the uselessness of an organic approach to this disease and illustrating the remarkable effect of the release of severe emotional tensions in the rapid and permanent cure of this condition is presented.

ABSTRACT OF DISCUSSION

DR. CARROLL S. WRIGHT, Philadelphia: Cheilitis glandularis is generally regarded as of unknown etiology. When we are confronted with a disease for which there is no known cause I am glad to see someone have enough courage to offer a tentative solution, and for doing so I wish to congratulate Drs. Woodburne and Philpott. As a matter of fact, all the textbooks that I had in my office listed the condition as a disease of unknown cause. Cheilitis glandularis is an extremely rare disease, and to be able to study even three cases intensively represents a feat. I was unable to find records of my having seen more than three cases in the 28 years I have been in practice in Philadelphia. Of course, all of these were seen a number of years ago before we had heard of such a thing as psychosomatic medicine.

One case was of particular interest. The patient was a nun, and according to a note on her chart she was emotionally upset. At the time, I assumed that her emotional condition was caused by her lip involvement. She was the only one

of the three patients I considered cured; we put her into the hospital, cauterized her lip and produced a scar. It is hard to know what we might have been able to accomplish in a case like that by psychiatric means.

We know that this disease represents an inflammatory overactivity of the mucous glands of the lips. We also know that other glands, notably the sweat glands, and to a less extent, the sebaceous glands, are influenced by psychic disturbance. It is reasonable to believe that the mucous glands of the lips may be likewise influenced by emotional upsets.

In preparation for my talks on psychosomatic medicine in relation to dermatology I have reviewed the literature extensively but have never seen mention of cheilitis glandularis falling into the group of psychosomatic disorders. I never found cheilitis glandularis mentioned in any of the papers that have been written on the subject. I feel that this theory is plausible, and Drs. Woodburne and Philpott would seem to have supportive evidence for their theory. It is to be hoped that, in view of the rarity of this disorder, others will study the cases that may come their way along the lines suggested by the authors. It will require additional evidence to prove the theory.

Dr. Francis A. Ellis, Baltimore: I was very interested in hearing the presentation on cheilitis glandularis. I have seen several cases and was in doubt as to just where to classify them. One case that I saw was also in a nun, a teacher who was incapacitated for about 10 years. Many types of local therapy were tried, until eventually she was treated with radical plastic surgery. The entire mucous membrane of the lips was removed and the patient had surgical treatment on the muscles to give a "proper balance" to what remained of the lips. The results were so excellent that she was able to return to teaching. Another patient had only partial involvement of the upper lip. The affected area was fairly deeply desiccated, but there was a recurrence. Plastic surgery was advised. Personally, I am somewhat skeptical of the theory of psychogenic etiological factors.

Dr. George M. Lewis, New York: The differential diagnosis may be rather difficult for some of these patients. Contact dermatitis may simulate closely the disease under discussion, and seborrheic dermatitis, moniliasis and other diseases may be considered. In two cases that were studied carefully and in which there was every reasonable belief that the differential diagnosis finally narrowed down to cheilitis glandularis there was evidence that considerable emotional instability was present both in the patient and in the family. In both instances there was either a family or a personal history of atopy. It is conceivable, then, that cheilitis glandularis is not a disease *sui generis* but another example of a name given to a condition which, after all, may be nothing but a variant of neurodermatitis (atopic eczema).

In further support of this hypothesis antihistamine drugs were tried in treatment of both of the patients. In one patient the antihistamine drug was given locally, and in the other patient antihistamine therapy was administered orally. In both cases there was a rather spectacular disappearance of the eruption, and with continued therapy the eruption stayed away. This response was similar to that expected in atopic eczema.

Dr. A. R. Woodburne: The patient in case 2, with whose case we spent the most time, was carefully followed in a rigorous elimination routine while in the hospital, and we were never able to feel that either ingested or contact allergens influenced the picture at all. I am happy to hear that the antihistamine drugs have been of benefit, and, if this young lady has any trouble again or if we have other cases of this condition, I shall certainly be interested in trying them.

DRYNESS OF THE MOUTH

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OAKLAND, CALIF.

AS DERMATOLOGISTS we are frequently concerned with complaints referable to the mouth and with changes in the oral mucous membranes. Deficiency or absence of saliva may result in changes in the oral mucosa with which we should all be familiar.

When the quantity of saliva secreted is moderately reduced the mucous membranes may appear normal. The salivary deficiency may be evident only in that the saliva is always mucoid, sticky, weblike, bubbly and frothy rather than thin and watery. It may be adherent and ball up and be difficult to expectorate without the moistening of the mouth with water. Burning and paresthesias of the oral mucosa, particularly of the tongue, are common symptoms and may at times precede the onset of recognized salivary deficiency.

Pronounced deficiency or complete absence of saliva leads to stickiness, dryness, soreness, burning and pain of the mucous membranes and to redness, atrophy, loss of papillae, fissuring and, at times, scaling and superficial crusting of the tongue. In severe cases denudation may occur so that the tongue looks like "raw meat." The rest of the mucous membranes may show similar changes or may be dry, smooth, pale and semitranslucent. Coincident general illness or nutritional deficiency may contribute to the local picture.

In almost all cases of pronounced lack of saliva rapid deterioration of the teeth develops, with extensive caries and ultimate loss. This is unfortunate because it is often difficult and uncomfortable for these patients to wear dental plates. The lips may also show similar changes, with dryness, varying degrees of inflammation, scaling and fissuring. Fissuring at the corners of the mouth is common. The patient may note first that the mouth becomes dry when he is speaking unless liquids are sipped at frequent intervals. It may be necessary for him to keep water by the bed and sip it at night to prevent the tongue from adhering to the palate and to keep the lips from becoming stuck together. Chewing

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and swallowing are frequently difficult unless the mouth and throat have first been moistened. Choking may occur unless the food is liquid.

Without debilitating general disease lack of saliva appears to cause very little adverse affect on health. This was true of the patient reported by Bartley [1] in the earliest reference I found to mouth dryness. Many persons with the condition have lived for years, apparently suffering only inconvenience and annoyance as a result.

Dryness of the mouth is commonly associated with lessened secretion of tears and dryness of the eyes. In pronounced cases these manifestations lead to changes in the conjunctivas and corneas known as keratoconjunctivitis sicca. Although this paper is primarily concerned with mouth dryness a great deal of the material discussed applies to both mouth and eyes.

Of the principal salivary glands the parotid contains only cells capable of secreting a thin, watery, serous fluid poor in organic material but rich in enzymes.[2] The alveoli of the submaxillary gland are of two types. Some contain serous cells, and some, mucous cells which produce a thick, slimy, viscid juice rich in mucin and organic materials. The sublingual glands are also mixed but are primarily mucous. A smaller amount of primarily mucoid secretion is produced by the mucous and some seromucinous glands which occur in the cheek, the lip, the palate and the tongue.

The salivary and lacrimal glands are supplied with secretory nerves from both the bulbar and the thoracolumbar divisions of the autonomic nervous system.[2] Certain areas of the cerebral cortex probably exert some regulatory influence over the sympathetic and parasympathetic systems and thus over salivary flow.[3]

The bulbar autonomic nerve supply arises from areas in the floor of the medulla oblongata called the salivary nuclei. The submaxillary, sublingual and lacrimal glands receive their bulbar nerve supply from the superior salivary nucleus. The parotid receives its bulbar innervation from the inferior salivary nucleus. Stimulation of this bulbar supply results in activity in the acini composed of the serous cells and a pouring forth of a large amount of thin, watery saliva and of tears. Vasodilation also results.

The thoracolumbar or sympathetic supply of all three of the salivary glands and the lacrimal gland is from the upper one or two thoracic segments of the cord and the superior cervical ganglion by way of the

1. Bartley, A. G.: Case of Suppressed Salivary Secretion, M. Times & Gaz. **54**:603 (Nov. 21) 1868.

2. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 5, Baltimore, Williams and Wilkins Company, 1950, p. 49.

3. Furstenberg, A. C., and Crosby, E.: Disturbance of the Function of the Salivary Glands, Ann. Otol., Rhin. & Laryng. **54**:243 (June) 1945.

plexuses of the external carotid artery. Stimulation of the sympathetic supply results in smaller amounts of a thick mucoid saliva from the submaxillary and sublingual glands (none from the parotid, since it contains only serous cells, and none from the lacrimal glands). Vasoconstriction also results.

Although the secretion of the salivary glands is controlled by the autonomic nervous system the salivary cells are susceptible to chemical influences. It is now known that autonomic effects are associated with the liberation of chemical substances at the nerve terminals.[4] These substances include acetylcholine, sympathin and, perhaps, histamine. It is probable that these substances may at times reach the salivary glands by way of the blood stream and stimulate secretion by a hormonal action. Metabolic disturbances and drugs affecting the function of these chemicals and the enzymes which destroy them can influence salivary secretion.

Faber,[5] who has published several excellent articles on the subject of dry mouth, used two methods of measuring salivary secretion. One consisted in having the patient hold a lump of sugar beneath the tongue without chewing, swallowing or moving the tongue and then noting the time required for the sugar to dissolve. In young normal persons this time is an average of 15 minutes; in older persons, 20 to 25 minutes, and in the very old, 30 minutes. The other method consisted in placing a small bifurcated glass suction apparatus beneath the tongue and measuring the saliva collected. Faber [6] showed that in patients with dry mouth the amylase content of the saliva which is present is reduced. The protein content, however, is higher in proportion to the reduction in the rate of secretion. These observations suggest that the serous secretion, especially that from the parotid, is affected first and foremost.

Lourie [7] worked with small flat suction disks which fit over the openings of Stensen's ducts with a minimum of irritation. The saliva secreted by the parotids was drained through small rubber tubes into measuring pipets. He and others showed that there is a slight, but measurable, continuous resting secretion of the salivary glands. There is temporarily a more rapid rate after rest periods, but on proper stimulation normal secretion may keep up undiminished for hours. Sleep and hypnosis inhibit secretion, and anesthetics tend to stop it although ether

4. Best and Taylor,[2] p. 1083.

5. Faber, M.: The Causes of Xerostomia, Acta med. Scandinav. **113**:69, 1943.

6. Faber, M.: Protein and Amylase in the Saliva from Normal Individuals and from Patients with Xerostomia: Studies in Xerostomia, Acta med. Scandinav. **118**:457, 1944.

7. Lourie, R. S.: Rate of Secretion of the Parotid Glands in Normal Children: Measurement of Function of Autonomic Nervous System, Am. J. Dis. Child. **65**:455 (March) 1943.

and chloroform may cause an increased amount during induction of anesthesia.

Minor emotional reactions cause slightly increased secretion. More intense emotional disturbances, such as fear, cause a temporary rise in rate and then inhibition of secretion. Disgust, embarrassment, pain and erotic emotions have a depressing effect while pleasurable sensations may increase the rate slightly. Mental work and concentration cause a decreased secretory rate in most subjects. Hunger and fasting inhibit parotid secretion, whereas satiation and distention of the stomach cause an increased rate.

Lourie [7] showed that the high rate of secretion present in early childhood (drooling) decreases rapidly from the age of 3 years to about 5 or 6 years and then more slowly until it approaches normal adult levels at the age of 11 or 12. In contrast to the high rate in childhood there is a lowering of activity in older age groups. This tends to parallel the decreased activity of other glands resulting in the hypochylia, dry skin and general atrophic changes of senility.

The great majority of reported cases of dry mouth have been in older persons, and this natural atrophic change probably is a contributing factor in many instances. Curschmann [8] and others have considered it a major cause in their classification of this disease.

The mouth may be temporarily dry even in the presence of normal salivary gland function. Persons whose work requires that they speak constantly and mouth breathers may note dryness of the lips and mouth and require sips of water for relief. This problem existed in the case of a young woman who talked over the telephone almost constantly in taking advertising for a local newspaper.

Congenital xerostomia (the name "xerostomia" was suggested independently by Hutchinson and by Hadden [9]) may occur because of hypoplasia or absence of the salivary glands. Harkin,[10] in a letter to the editor of *The Lancet,* quoted from an article which he wrote and which was published in *The Dublin Journal of Medical Science,* November 1880: "Salivary glands may fail in secreting power from congenital defects, as in a class recognized by naturalists as 'dry-mouthed families.'" Faber [11] reported a case of congenital xerostomia in a 13 year old boy and referred to nine other cases reported in the literature. He mentioned that in a few cases of hereditary ectodermal dysplasia notable reduction in salivary secretion was described.

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8. Curschmann, H.: Über Xerostomie, München. med. Wchnschr. **76**:269 (Feb. 15) 1929.

9. Hadden, W. B.: Xerostomia (Dry Mouth), Brain **11**:484, 1888-1889.

10. Harkin, A.: Suppression of the Salivary Secretion, Lancet **1**:257, 1888.

11. Faber, M.: A Case of Congenital Xerostomia, Acta pædiat. **30**:148, 1942.

Lisch [12] reported 12 cases of Sjögren's syndrome occurring in three generations of one family. In eight of these dryness of the mouth was present. He expressed the belief that these patients inherit some "idiopathic disposition to the disease."

More recently Coverdale [13] reported the occurrence of dryness of the mouth and eyes in a father and his daughter and in a mother and her daughter.

In most cases of local lesions only one of the salivary glands is involved and saliva from the others is adequate. This is usually true in tumor, obstruction (stone), acute suppurative infection or infiltration with such specific diseases as syphilis, tuberculosis and actinomycosis.[14]

However, in some such cases and in Mikulicz's disease, sarcoidosis (uveoparotid fever) and the lymphoblastomas so much salivary tissue may be destroyed that mouth dryness results.[15] This may also occur if surgical removal or roentgen ray or radium damage is too extensive. Mouth dryness secondary to roentgen ray treatment for hypertrichosis is reported.[16]

During its acute stage mumps, especially in older persons, may cause a temporary inhibition of saliva, but apparently it does not cause permanent mouth dryness.[5]

Organic lesions of the nervous system which irritate or interrupt the central pathways of the secretory nerves can occasionally inhibit salivary secretion. Furstenberg and Crosby [3] discussed this possibility. According to them, when this occurs the disturbed salivary function is usually an incidental observation and is overshadowed by other more significant and conspicuous neurological signs. Curschmann [8] reported a case of a 57 year old man in whom failure of the salivary secretion was the first symptom of the development of an organic disease of the central nervous system, probably multiple sclerosis, with lesions involving the medulla oblongata.

Furstenburg and Crosby [3] described a group of patients in whom the secretory nerves were apparently defective, a condition which was probably a disturbance in the end organs. This possibility was indicated by

12. Lisch K.: Über hereditäres Vorkommen des mit Kerato-Conjunctivitis sicca verbundenen Sjögrenschen Symptomenkomplexes, Arch. f. Augenh. **110**:357, 1937.

13. Coverdale, H.: Some Unusual Cases of Sjögren's Syndrome, Brit. J. Ophth. **32**:669 (Sept.) 1948.

14. Furstenberg, A. C.: The Parotid Gland: Its Common Disorders, J. A. M. A. **117**:1594 (Nov. 8) 1941. Morris, S. A.: Salivary Glands: Pathological Conditions Affecting Them, California & West. Med. **57**:190 (Sept.) 1942.

15. Faber, M.: Om xerostomia, Nord. med. (Hospitalstid.) **14**:1856 (June 20) 1942.

16. Greenbaum, S. S., and Tumen, H. J.: Severe Xerostomia from X-Ray Treatment for Hypertrichosis, J. A. M. A. **107**:1297 (Oct. 17) 1936.

the improvement that these persons showed on administration of pilocarpine. The authors stated the belief that in some of these patients sufficient pilocarpine given over a long enough time would restore normal salivary function. This action of pilocarpine is enhanced by keeping the patient in a mild state of acidosis through restriction of alkalis in the diet and the administration of ammonium chloride. This result is due to the fact that acetylcholine acts best in an acid medium.

It is well known that drugs may cause a temporary dry mouth. Atropine is employed in anaesthesia both for its effect on the cardiovascular system and for the purpose of drying up the secretions of the salivary glands and mucous glands of the respiratory tract. Opium and its derivatives and ergotamine also inhibit salivary secretion.

Toxic agents such as organic dusts and zinc poisoning are suggested as possible causes of the condition by Furstenberg and Crosby.[3] They mentioned botulism as a cause.

Lourie,[7] Krasnogorski [17] and others showed that there is a decided correlation between the rate of secretion of saliva and general behavior in children. They expressed the belief that both are largely determined by the balance between cerebral function and subcortical activities. When these are ideally coordinated normal motor, secretory and emotional reactions result. In fact, salivary secretory rate has been suggested as of prognostic significance in behavior problems.

In postencephalitic patients the characteristic impulsiveness, aggressiveness and overactivity correlate with the drooling of excessive saliva as signs of regression to a lower level of cortical function.

Excessive salivary flow was noted in dementia paralytica many years ago by Hutchinson,[18] in the late psychotic stage of schizophrenia by Strongin and Hinsie [19] and in microcephalic children. Depressed salivary rates occur in early schizophrenia when patients are tense, anxious, worried and still trying, at times, to face reality and in the depressions of the manic-depressive type (caused by overactivity of the higher brain centers ?).

In one of the earliest reports of a case of dry mouth Jonathan Hutchinson [18] noted that the difficulty developed shortly after a deep emotional shock. He stated "The condition appeared to me to be an exaggeration, assuming permanency, of the state of mouth which is common under the emotion of fear and during states of nervous excitement." Many authors have since then noted the association of dry mouth

17. Krasnogorski, N. I.: Physiology of Cerebral Activity in Children as a New Subject of Pediatric Investigation, Am. J. Dis. Child. **46**:473 (Sept.) 1933.

18. Hutchinson, J.: A Case of "Dry Mouth" (Aptyalism), Tr. Clin. Soc., London **21**:180, 1888.

19. Strongin, E. I., and Hinsie, L. E.: Parotid Secretory Rate in Schizophrenic Patients, J. Nerv. & Ment. Dis. **87**:715 (June) 1938.

with nervous stress and strain, depression, hysteria and emotional disturbances of various types. In some the failure of salivary secretion has developed suddenly after emotional shock. Hadden,[20] Rowlands,[21] Fraser [22] and Mracek [23] all reported such cases. Curschmann [8] reported the cases of a singer, a musician and a lecturer who could perform satisfactorily among friends or before small audiences but whose mouths would become so dry before large or difficult groups or in solo work that they could not go on. These patients showed other signs of autonomic instability including nervous tachycardia and arrhythmia, trophic edema, dermographia, flushing, sexual neurasthenia, obstipation and periods of depression. He expressed the opinion that these patients had psychogenic dry mouth and gave them the name "xerophobes." Dr. Burton W. Adams, Oakland, Calif., with whom I have discussed this problem, said that he believes such cases are usually examples of psychasthenia, conversion hysteria or, occasionally, a neurotic picture in the setting of senility.

Dehydration alone can cause a pronounced depression in salivary flow. Winsor [24] found in human volunteers that thirst for 70 hours reduced salivary secretion to about one-sixth normal rate. Profuse sweating in a hot bath for one hour reduced secretion by 50 per cent. Gregersen and Bullock [25] also found that salivary secretion was reduced as the blood volume decreased when fluids were withheld.

Water loss through hemorrhage, excessive sweating, diarrhea and/or vomiting may be a cause of temporary mouth dryness. This symptom accompanies the excessive urinary output and thirst of diabetes mellitus and insipidus.

We are all familiar with the parched lips and dry mouth in most acute febrile diseases. Here elevated temperature, increased respiratory rate, perspiration and dehydration due to inability to take or retain fluids may combine to cause mouth dryness. It may be a symptom in liver and kidney diseases and in cardiac decompensation.

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20. (*a*) Hadden [9]; (*b*) On "Dry Mouth," or Suppression of the Salivary and Buccal Secretions, Tr. Clin. Soc., London **21**:176, 1887-1888.

21. Rowlands, W.: Permanent Suppression of the Salivary Secretion (?), Lancet **1**:104 (Jan. 14) 1888.

22. Fraser, T. R.: Xerostomia (Mouth-Dryness) with Dryness of the Nose and Eyes, Edinburgh Hosp. Rep. **1**:149, 1893.

23. Mracek, F.: Die Erkrankungen der Mundhöhle, Spec. Path. u. Therap. **16**(pt. 1):83, 1902.

24. Winsor, A. L.: The Effects of Dehydration on Parotid Secretion, Am. J. Psychol. **42**:602 (Oct.) 1930.

25. Gregersen, M. I., and Bullock, L. T.: Observations on Thirst in Man in Relation to Changes in Salivary Flow and Plasma Volume, Am. J. Physiol. **105**:39, 1933.

Dietary and vitamin deficiencies can apparently cause not only inflammatory and atrophic changes in the mucous membranes but atrophy and failure of secretion of the salivary and lacrimal glands, also. Chamberlin [26] reported a case which suggests this etiology. Von Grósz [27] expressed the opinion that a disturbance of vitamin metabolism could be responsible.

Lyon [28] stated the belief that the parotid gland swelling and lessened secretion of saliva which have been reported by many as occurring in diabetes, thyroid disturbance, genital atrophy, starvation and alcoholism are due to vitamin A deficiency. He described transitory aptyalism brought on by sudden considerable loss of vitamin A through the use of general anesthesia or through infection. He expressed the opinion that this observation may help to explain certain cases of postoperative parotitis.

Lyon [28] cited Stepp, Kühnau and Schroeder [29] as stating that in animals vitamin A deficiency causes keratinization of the epithelium of the ducts with retention of the secretion of the salivary glands and the frequent formation of abscesses. Similar inflammatory reaction and "keratinizing metaplasia" of the salivary glands and ducts were reported in humans by Wolbach [30] and by Wilson and DuBois.[31]

Stahel [32] gave a number of reasons for his belief that vitamin A deficiency can cause xerostomia and keratoconjunctivitis sicca. Holm,[33] however, examined 50 keratoconjunctivitis sicca patients and found no evidence of vitamin A deficiency by dark-adaptation test.

Faber [5] stated the belief that some of the so-called idiopathic cases of dry mouth are due to ariboflavinosis. He noted that Lundh and Geill's [34] description of patients whose condition improved under ribo-

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26. Chamberlin, W. B.: Xerostomia: Is It a Deficiency Disease? J. A. M. A. **95**:470 (Aug. 16) 1930.

27. von Grósz, S.: Aetiologie und Therapie der Keratoconjunctivitis sicca, Klin. Monatsbl. f. Augenh. **97**:472 (Oct.) 1936.

28. Lyon, E.: Swelling of the Parotid Gland and Diabetes Mellitus, Gastroenterologia **68**:139, 1943.

29. Stepp, W.; Kühnau, J., and Schroeder, H., Die Vitamine und ihre klinische Anwendung: Ein urzer Leitfaden, Stuttgart, Ferdinand Enke, 1936, p. 10.

30. Wolbach, S. B.: The Pathologic Changes Resulting from Vitamin Deficiency, J. A. M. A. **108**:7 (Jan. 2) 1937.

31. Wilson, J. R., and DuBois, R. O.: Keratomalacia in Infant, with Postmortem Examination, Am. J. Dis. Child. **26**:431 (Nov.) 1923.

32. Stahel, W.: Das Sjögrensche Syndrom eine A-Hypovitaminose, Klin. Wchnschr. **17**:1692 (Nov. 26) 1938.

33. Holm, S.: Keratoconjunctivitis Sicca and the Sicca Syndrome, Acta ophth., 1949, supp. 33.

34. Lundh, B., and Geill, T.: Riboflavin—Avitaminosis (B_2 Mangel), Nord. med. **12**:3547 (Dec. 13) 1941.

flavin therapy corresponded closely to his of persons with xerostomia. He reported pellagra and a dry mouth in a patient with anorexia nervosa whose condition improved with the administration of the vitamin B complex plus riboflavin. The tongue has been noted as being dry at times in nicotinic acid deficiency.[35] Saphir [36] reported treating xerostomia successfully with nicotinic acid. However, both salivation and lacrimation are noted at times in riboflavin and nicotinic acid deficiencies.

Von Grósz [27] noted xerostomia in association with pernicious anemia. In nine untreated cases of pernicious anemia studied by Faber [5] five patients showed reduced salivary secretion. He stated the opinion that dry mouth is also common in iron deficiency anemias. He cited Markoff [37] as reporting lack of saliva in cases of sprue. Holm [33] reviewed the opinions of several authors regarding the association of xerostomia and keratoconjunctivitis sicca with sideropenia and the Plummer-Vinson syndrome. He concluded that although these conditions occur together frequently there is no clear etiological relationship.

Many have considered that mouth dryness might result from an endocrine gland disturbance. This is suggested by what Holm [33] called the "enormous sex specificity of xerostomia [for women] with a predilection for the climacteric." Titration studies in some of his cases of keratoconjunctivitis sicca and xerostomia showed a tendency to reduced estrogenic hormone levels. Zweifel [38] expressed the belief that there is a noteworthy frequent coincidence of salivary gland disease and endocrine disturbance. He also reviewed evidence for and against an endocrine function of the salivary glands themselves.

Brückner [39] reported the case of a woman with dryness of the mucous membranes whose symptoms and signs cleared and were subsequently controlled by the administration of testosterone propionate (perandren,® Ciba) but recurred when it was discontinued.

Reviews of this subject (dry mouth) have been published by Fraser,[22] Chappell,[40] Fellenz,[41] Schmidhuber,[42] Glasscheib [43] and others. They

35. Bicknell, F., and Prescott, F.: The Vitamins in Medicine, ed. 2, New York, Grune and Stratton, Inc., 1946, p. 335.

36. Saphir, W.: Xerostomia Successfully Treated with Nicotinic Acid, Am. J. Digest. Dis. **7**:298 (July) 1940.

37. Markoff, N. G.: Die einheimische Sprue, Helvet. med. acta (supp. 3) **5**:3 (Sept.) 1938.

38. Zweifel, E.: Beobachtungen bei Speicheldrüsenerkrankungen, Helvet. med. acta **12**:619 (July) 1945.

39. Brückner, R.: Über einen erfolgreich mit Perandren behandelten Fall von Sjögren'schem Symptomenkomplex, Ophthalmologica **110**:37 (July-Aug.), 1945.

40. Chappell, W. F.: Report of 3 Cases of Xerostomia, or Dry Mouth, New York M. J. **63**:277 (Feb.) 1896.

41. Fellenz, J. A.: Über Xerostomie, Inaug. Dissert., Heidelberg, J. Hörning, 1903.

(Footnotes continued on next page)

mentioned additional causative factors such as influenza, general illness, poor mouth hygiene, dental caries, early loss of teeth, accommodation to set of false teeth, physical trauma (blow on the head), pregnancy and reflex nervous disturbance (salivary stone). Probably most, if not all, of these observations are coincidental and not of important etiological significance.

Dryness of the mouth alone can be relieved temporarily by frequently sipping liquids and, while a distressing nuisance, rarely interferes with vital functions. When pronounced dryness of the conjunctiva as a result of failure of the secretion of tears occurs, discomfort may be severe and visual disturbance may develop. Many of the patients with this disorder, therefore, have been studied by ophthalmologists. A Swedish ophthalmologist, Henrik Sjögren, reviewed this subject in a series of articles which appeared beginning in 1933.[44] The first of these has since been translated into English by Hamilton.[45] These concerned a group of patients which he believed represented a separate syndrome which he first called "keratoconjunctivitis sicca." Later the term "stomatokeratoconjunctivitis sicca" was applied. More recently Sjögren proposed the name "Dacryo-sialo-adenopathia atrophicans."[46] It is most often designated as "Sjögren's syndrome" or the "sicca syndrome."

Faber found associated lacrimal deficiency in about one third of the cases of xerostomia which he studied.[47] He expressed the belief that many of the cases of "idiopathic" xerostomia are examples of Sjögren's syndrome. In 12 of Holm's 21 cases of keratoconjunctivitis sicca occurring in nonrheumatic patients there was also xerostomia.[38] Nine of Sjögren's first 19 patients with keratoconjunctivitis sicca showed coincident salivary failure.[44] Sjögren stated the opinion that the mouth or the eye symptoms predominate according to whether the salivary or the lacrimal glands are most affected.

The eye changes and associated observations in Sjögren's syndrome were presented in Sjögren's papers and subsequently by others including

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42. Schmidhuber, K. F.: Ein Beitrag zur Klinik der Xerostomie, München. med. Wchnschr. **69**:1406 (Sept.) 1922.

43. Glasscheib, A.: Zur Aetiologie und Klinik der Xerostomie, Monatschr. f. Ohrenh. **64**:1377 (Dec.) 1930.

44. Sjögren, H.: Zur Kenntnis der Keratoconjunctivitis sicca (Keratitis filiformis bei Hypofunktion der Tränendrusen), Acta ophth. 1933, supp. 2, p. 1.

45. Sjögren, H.: A New Conception of Keratoconjunctivitis Sicca, translated by J. Bruce Hamilton, Sidney, Australasian Medical Publishing Company, Ltd., 1943.

46. Sjögren, H.: Zur Kenntnis der Keratoconjunctivitis sicca; das Siccasyndrom und ähnliche Zustände: Dacryo-Sialo-Adenopathia atrophicans, Acta ophth. **18**:369, 1940.

47. Faber, M.: The Frequency of Reduced Lacrymal Secretion in Xerostomia, Acta med. Scandinav. **118**:452, 1944.

Bruce,[48] Gifford, Puntenney and Bellows,[49] Lutman and Favata[50] and Ellman and Parkes Weber,[51] in the monograph by Holm[33] and by Behrman and Lee.[52] In these cases, too, postmenopausal women were most frequently involved.

In addition to there being varying degrees of conjunctivitis and keratitis and xerostomia in this syndrome, the mucous membranes of the nose, pharynx and larynx and, at times, the vulva and vagina may be dry and atrophic.

Sjögren expressed the belief that the mucous membrane lesions are only a part of a general disease picture.[53] He noted that many of the patients were pale, thin and asthenic; they looked sick and were "older" than their chronologic age. Various writers described the frequent occurrence in these cases of low grade fever, rapid blood sedimentation rate, anemia, relative lymphocytosis, impaired sugar tolerance, deficient gastric secretion, foci of infection and, above all, arthritis.

Sixty per cent of Sjögren's 62 patients with keratoconjunctivitis sicca showed contemporary arthritis.[54] Holm[33] examined 500 rheumatic persons (440 with polyarthritis rheumatica chronica and 60 with rheumatic fever) and found that approximately 20 per cent showed well established or incipient keratoconjunctivitis sicca and another 20 per cent showed probable incipient signs of this condition. He expressed the opinion that there is an important etiological relationship between arthritis and the sicca syndrome. In Holm's arthritis cases men showed keratoconjunctivitis sicca almost as frequently as women.

Dryness of the skin, reduced sweating, circulatory disturbances of the extremities similar to Raynaud's disease and pigmentation and sclerodermatous changes in the legs have been reported as associated observations.[55]

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48. Bruce, G. M.: Keratoconjunctivitis Sicca, Arch. Ophth. **26**:945 (Dec.) 1941.

49. Gifford, S. R.; Puntenney, I., and Bellows, J.: Keratoconjunctivitis Sicca, Arch. Ophth. **30**:207 (Aug.) 1943.

50. Lutman, F. C., and Favata, B. V.: Keratoconjunctivitis Sicca and Buccoglossopharyngitis Sicca with Enlargement of the Parotid Glands: Report of Two Cases of Sjögren's Syndrome, with Pathologic Study of Lacrimal Gland and Parotid Glands in One Case, Arch. Ophth. **35**:227 (March) 1946.

51. Ellman, P., and Weber, F. P.: Sjögren's Disease, with Dryness of the Bronchial Mucosa and Uncertain Lung Lesion, British M. J. **1**:304 (Feb. 19) 1949.

52. Behrman, H. T., and Lee, K. K.: Sjögren's Syndrome, Arch. Dermat. & Syph. **61**:63 (Jan.) 1950.

53. Sjögren, H.: Zur Kenntnis der Keratoconjunctivitis sicca: Allgemeine Symptomatologie und Ätiologie, Acta ophth. **13**:1, 1935.

54. Sjögren, H.: Keratoconjunctivitis Sicca and Chronic Polyarthritis, Acta med. Scandinav. **130**:484, 1948.

55. Sheldon, J. H.: Sjögren's Syndrome Associated with Pigmentation and Sclerodermia of the Legs, Proc. Roy. Soc. Med. **32**:255 (Feb.) 1939.

Swelling of the parotid glands is given as a common feature of Sjögren's syndrome. However, Sjögren apparently considered this due to infection secondary to failure of the protective effect of a normal salivary flow.[46]

The patients whose cases I shall report all complained of dryness of both the mouth and the eyes and presented, I believe, classic examples of Sjögren's syndrome.

REPORT OF CASES

CASE 1.—M. F. A., a white woman, acquired dryness of the mucous membranes of the mouth and eyes at the age of about 54 while suffering from a progressive cirrhosis of the liver, from which she died at the age of 56. The dryness of both the mouth and the eyes increased so that finally only sticky mucoid secretion was present. The patient was unable to wear her dentures and could eat no dry food. Burning and irritability of the eyes made it impossible for her to read. It was necessary for her to use a solution simulating tears frequently as eye drops. Examination by an otorhinolaryngologist late in the course of the disease showed atrophy of the salivary and lacrimal glands and pronounced dryness of the mucosae. There were chronic conjunctivitis and keratitis but no corneal ulceration.

The past history revealed typhoid in early adult life. The patient had chronic constipation relieved by frequent enemas. A hemorrhoidectomy was performed at the age of 49, and menstruation was stopped at 50 by uterine curettage and the application of radium because of menorrhagia and metrorrhagia. The patient had otherwise been in good health until generalized itching and jaundice called attention to the developing cirrhosis of the liver at the age of 53. This progressed steadily with enlargement of the spleen, ascites, dependent edema, hydrothorax and death following intestinal hemorrhage.

A wide variety of treatment including dietary management and large doses of the vitamin B complex and vitamin A were given, to no avail.

During the course of the disease there developed anemia which was at times severe. The prothrombin time also became lowered, and transfusions were given. The blood sedimentation rate was consistently elevated. The amount of blood proteins, particularly the serum albumin, tended to be low. The amount of blood cholesterol during most of the course of her disease was decidedly and consistently elevated, reaching as high as 812 mg. per 100 cc. in August 1946. Later it became lower, and her last hospital entry, in March 1947, it was 212 mg. per 100 cc. Reactions to Van den Bergh tests done early in the disease were positive (direct). The icteric index rose steadily, and terminally it was 120 units.

Autopsy showed the picture of an advanced cirrhosis of the liver with congestion, vascular dilatation and adhesions to surrounding organs. There were hyperemia and distention of the vessels of the intestinal tract with evidence of recent hemorrhage. There were moderate ascites and a pronounced bilateral hydrothorax. The liver and spleen were both enlarged. The liver microscopically showed the changes characteristic of a chronic periportal hepatitis and cirrhosis. The spleen showed evidence of chronic congestion. The pancreas showed evidence of recent acute pancreatitis together with a moderate degree of long-standing chronic interstitial pancreatitis.

The cardiovascular and urinary system showed no important change. The adrenal glands and the genital system were reported as normal. Unfortunately for the purposes of this paper no examination of the mucous membranes or lacrimal or salivary glands was made.

CASE 2.—A. G., a white spinster aged 66, was first seen by me on Nov. 18, 1946. She was presented before a joint meeting of the San Francisco, Los Angeles and Pacific Northwest Dermatological Societies with the diagnosis of Sjögren's syndrome on Jan. 18, 1947.[56] She first noted that her mouth was dry at about the age of 50, when she began to have to sip water frequently in order to be able to continue talking in the course of her work. Sticky, tenacious mucus would at times collect in her mouth and be difficult to dispose of. Her eyes began to feel dry and irritable several years later. Since the age of 58 she had had no tears on weeping.

She had had the usual childhood diseases, including mumps. She had had pneumonia and erysipelas when quite young but had been generally a healthy child.

She had had a "nervous breakdown" at the age of 26, and when she was 57 a diagnosis of "nervous exhaustion" had been made.

A fibroid tumor of the uterus had been removed at the age of 36, and a tonsillectomy done when the patient was 45.

She had acquired arthritis affecting particularly the neck and shoulders at the age of 53. This had become so severe as to necessitate her wearing a brace for six months. Recently she had had only minor soreness of her joints, mostly of the fingers, hands and knees.

She had had variable hypertension with a systolic pressure of 220 at times for the past six to eight years.

She had begun menstruating at the age of 13. Her periods were normal and regular until shortly prior to the menopause, when for a time she had an excessive flow. This was controlled by orally administered medication, including thyroid. Her menopause was normal and occurred at about the age of 53 years.

Family history revealed that her father had complained at times of dry lips, cause unknown.

Eye examination by Dr. J. R. Sharpsteen, Oakland, Calif., in November 1947 showed a Schirmer test result (moistening of a standard piece of filter paper one end of which is placed in the eye) of 7 mm. in five minutes (normal 21 to 25 mm.). Her eyes were otherwise normal. Her lacrimal glands were not palpable. Her submaxillary salivary glands were small but palpable and were not tender. Her mouth was notably dry, especially after a few moments of talking.

The administration of vitamin A concentrate, 75,000 units daily, orally, for three months was not helpful.

After this treatment and in accordance with the procedure outlined by Friedman and Gernand,[57] diethylstilbestrol was prescribed. Although it was given until menstrual bleeding resulted, no appreciable benefit of the dryness of the mouth or eyes resulted.

Early in 1949 the patient, after a severe upper respiratory tract infection, acquired otitis media which cleared after myringotomy.

The result of Schirmer's test done in March 1950 again showed 7 mm. of moistening in five minutes bilaterally. A lump of sugar placed under the tongue dissolved in 45 minutes on one occasion and was not yet dissolved in an hour on another trial.

Dr. Nelson S. Keeler, Oakland, Calif., recently examined the patient and noted that the oral mucous membrane showed little change but was generally sticky and

56. Allington, H. V.: Sjögren's Syndrome (Case Report), Arch. Dermat. & Syph. **60**:1050 (Nov.) 1949.

57. Friedman, B., and Gernand, H.: Sjögren's Syndrome Treated with Stilbestrol: Report of Case, California & West. Med. **64**:31 (Jan.) 1946.

covered thinly by bubbly, frothy mucus. The mucosa of the nose was slightly inflamed and glazed.

Pelvic examination by Dr. T. Floyd Bell, Oakland, Calif., and microscopic examination of stained vaginal smears showed the changes of estrogen deficiency to be expected at the patient's age. There was very little secretion of any kind.

Physical examination revealed an otherwise essentially normal condition except for arthritic changes in the small joints of the fingers.

Recently blood studies showed normal bleeding and clotting time and platelet counts. Hemoglobin and red blood cell counts were normal. The leukocyte count was slightly low (4,450 per cubic millimeter), and there was relative lymphocytosis (56 per cent). Blood proteins and the albumin-globulin ratio were normal.

Blood amylase was low (37 mg. per cent).

The results of the trypsin test (liquefaction of gelatin film) suggested low trypsin content in the feces. The cephalin flocculation test gave a negative reaction at 48 hours. The result of the sulfobromophthalein excretion test was normal. Gastric analysis showed free hydrochloric acid to be present. The result of the 17-ketosteroid assay was 7.0 mg. per 24 hours, (normal, 6 to 13 mg. per 24 hours).

Testosterone propionate, 25 mg. given intramuscularly three times weekly, was recently given for three weeks without change in the mouth or eyes.

CASE 3.—G. P., a 70 year old white woman, was seen on Dec. 10, 1946, at the age of 66, because of small, smooth, pale yellowish papular elevations (traumatic fibromas) present on the buccal surfaces along the line of closure of the teeth. These appeared to be related to the fact that she frequently drew in her cheeks and lips in a sucking grimace in an apparent attempt to draw saliva into her mouth.

Her mouth had been notably dry since she was about 45. She would choke if she attempted to chew and swallow crackers or other dry food. At about the age of 50 she had first acquired intermittent swelling in the region of the right parotid. Since the age of 55 she had had to sip water frequently, including several times throughout the night, to keep her mouth from becoming parched.

At about the age of 20 her eyes had begun to burn and sting. They often felt as though they had hot sand in them. Reading by artificial light made them worse. The patient also noted that she produced less tears than normal.

She had been a very thin and sickly child. She had always been constipated. She had had frequent "head colds and sinus trouble" and many sore throats. She had had measles, whooping cough, chickenpox, diphtheria and typhoid before she was 12, but had escaped mumps.

She had begun having "pyorrhea" at the age of 20 and had required frequent dental attention ever since. She had had two nasal operations because of continuing "sinus trouble." When she was 47 her tonsils were removed and a small benign tumor was removed from the neck of her bladder. She had had frequent attacks of laryngitis and bronchitis. A hemorrhoidectomy was performed when she was 57.

She had begun to menstruate at 18. The flow was always scanty. She had had a spontaneous menopause at 47. She had married at 36 and was never pregnant.

From the age of 12 she had had many attacks of a dermatitis of the exposed skin surfaces which seemed to be provoked by exposure to sunlight. Recently, since avoiding fish in her diet, she has had no further recurrences.

At the age of 60 she was treated for dry, brittle nails and for chronic paronychial infection. The basal metabolic rate was —18 per cent. The patient was given thyroid and multivitamin therapy including the administration of 100,000 units of vitamin A for a period of five months without change in the character of her nails or in the dryness of her mouth or in the eye symptoms.

She had been treated intermittently throughout most of her life for mild anemia. She said she believes that she perspires less than normal except on her scalp, where there is excessive sweating.

The patient's mother is said to have had a dry mouth for much of her life and to have lost all her teeth by the age of 34.

A diagnosis of Sjögren's syndrome was made on Feb. 20, 1947, and diethylstilbestrol was prescribed. It was given for a period of five weeks to the point of producing vaginal bleeding. There was no apparent change in the mucous membrane symptoms, however.

The patient reported to Dr. Karl Deissler, Oakland, Calif., in January 1949. He, independently, arrived at a diagnosis of Sjögren's syndrome. He noted a conjunctivitis sicca without corneal lesions, a rhinitis sicca with crusting in the nasal passages and chronic sinusitis and the dry mouth. He found that the patient had gastritis simplex and diverticulosis with recurrent diverticulitis. Allergic study including both scratch and intradermal testing gave negative results.

In January 1950 the patient had a flare of arthritis of her wrists, which had been present in mild form since she was about 63. At this time she had more trouble with her mouth dryness and noted a mild recurrence of swelling in the right parotid gland. She believed this condition was due to nervousness and discomfort. Her mouth and eye symptoms had apparently been aggravated in the past by periods of increased nervous tension.

In April 1950 Dr. Sharpsteen found the corneas to be normal. Schirmer's test showed 8 mm. of moistening in the right eye and 12 mm. in the left after five minutes.

Dr. Nelson S. Keeler, Oakland, Calif., noted that the mouth appeared relatively normal except for dryness of its anterior portion. A lump of sugar under the tongue dissolved in approximately 25 minutes on two occasions.

Vaginal examination by Dr. T. Floyd Bell, Oakland, Calif., and a stained vaginal smear showed only the atrophic changes to be expected at 70 years of age.

Results of a recent urinalysis were normal. A blood count showed the erythrocyte count and amount of hemoglobin to be at the lower limits of normal. The leukocyte count was normal, but there was mild relative lymphocytosis. The platelet count and bleeding and clotting times were normal. The blood sedimentation rate was slightly elevated.

Gastric analysis showed free hydrochloric acid to be present. Results of a sulfobromophthalein test were normal. Total blood proteins and the albumin-globulin ratio were normal. Prothrombin time was normal, and the reaction in the cephalin flocculation test was negative. Blood serum amylase was normal.

A glucose tolerance test showed a flat curve and a delayed return to normal fasting level.

Results of a 17-ketosteroid assay were normal (6.8 mg. per 24 hours).

CASE 4.—B. K., a white woman aged 76, was first seen by me and a diagnosis of Sjögren's syndrome was made on Feb. 13, 1947. She had first acquired dryness of the mouth at about the age of 57. Since then she had had choking and difficulty in swallowing and had had to "wash her food down." Her eyes, too, had been dry for many years. No tears had come when she cried. Tobacco smoke had caused pronounced burning and stinging but no tears.

These complaints followed the development of a throat abscess which was surgically drained. At about this time the patient had also acquired stomatitis following chewing eriodictyon (yerba santa). She had also been doing work involving unusual nervous tension and strain.

She had since had parotid swellings at times. These occasionally had followed minor trauma to the parotid region. They had apparently not been severe and were not accompanied with fever or malaise. She had had none for some months, however. She stated the belief that they stopped after the extraction of two infected molar teeth.

She had had measles, mumps, whooping cough and chickenpox in childhood. Her menses had begun at 13 and were at times accompanied with more than normal bleeding. Her menses had stopped at 42, after pelvic surgery.

A tonsillectomy was performed when she was 36.

At the age of 39 she had had pain and swelling in her left knee which was first thought to be tuberculous but which cleared after about seven months and was subsequently considered to have been arthritis. Recent roentgenograms have shown hypertrophic arthritis of the spine and of the fingers and left elbow.

She had a lifelong history of sinusitis, "catarrh" and bronchitis. She had had attacks of pneumonia at the age of 66 and at 70, and again two years ago at the age of 74. At the time of her last attack of pneumonia roentgenologic studies suggested probable bilateral basal bronchiectasis.

When the patient was 58, shortly after the mouth dryness began, Dr. Dorothy Allen, Oakland, Calif., found normal gastric analysis results, blood sugar and blood serum calcium. Basal metabolic rates varied between — 9 and — 20 per cent. The erythrocyte counts were normal, but hemoglobin averaged 65 per cent. There was no leukocytosis. Treatment with thyroid, iodine, liver extract, pilocarpine, strychnine, insulin and vitamins A and D was of no help at that time.

The patient was examined by Dr. H. Lisser, San Francisco, when she was 60. He found no endocrinopathy that could be linked with the xerostomia.

After the patient was first seen by me in 1947 estrogenic hormone treatment was given under the direction of Dr. Robert S. Peers, Oakland, Calif., with no change in the mouth or eye conditions.

During the past two or three years she has had occasional spells of cramping and loose stools. Gastrointestinal roentgenologic studies and fluoroscopic examination of the colon with the use of a barium enema revealed no abnormalities two years ago, however.

Recent examination showed a tall, spare woman who, in spite of her age and complaints, was alert and able to enjoy life. Objectively her eyes appeared normal. Her mouth always appeared dry. In speaking she did not enunciate clearly. It appeared as though she did not always use her tongue and lips effectively because of their dryness. The mucous membranes were not inflamed but appeared thin and shiny. The tongue appeared wrinkled, and the papillae, although present, were flattened and not normally filiform and velvety. No other important physical defects were noted.

Recent laboratory work showed a mild normochromic anemia with a normal leukocyte count and a normal differential count. Blood sedimentation rate and urinalysis were also normal. A Schirmer test done by Dr. J. R. Sharpsteen, Oakland, Calif., showed moistening of the filter paper of 17 mm. in both eyes. A cube of sugar placed under the tongue did not even lose its square shape in one hour.

Testosterone propionate, 25 mg. intramuscularly, was recently given three times weekly for three weeks without change in the amount of saliva or tears.

Case 5.—A. M. C., a white woman aged 71, was first seen for this complaint in the latter part of August 1949. Her mouth had begun to be dry at the age of 68, and her eyes, approximately a year later. Both gradually became worse until her mouth was so dry that she "could not lick a postage stamp." She was frequently bothered, especially at night, with sticky mucus which collected in her throat and

which she could "neither spit up nor swallow." Her nasal passages were dry and became "scabbed." Her eyes became so painful and sensitive to light that she kept her room darkened and wore heavy dark glasses during the day.

Late in 1949 examination showed the mucous membranes of the tongue, lips and buccal mucosa to be decidedly dry and reddened. The upper surface of the tongue appeared slightly thickened and wrinkled, but there were no erosions, fissures or crusting. There was pronounced atrophy of the papillae.

Dr. B. M. Stephens, Alameda, Calif., reported that the conjunctivas were dry and injected, and sticky, ropy mucus was present in the lower cul-de-sac. There were pronounced superficial corneal erosions, and at times epithelial filaments were present. Ointments appeared to give greater relief than "artificial tear" preparations tried.

The patient was a small, elderly, emaciated woman who showed decided limitation in motion of many joints and pronounced ulnar deformity of the hands. Her upper teeth were absent, and her lower ones were poor and extensively repaired. There was livido reticularis of the legs. Results of physical examination otherwise were essentially normal.

The past history revealed that the patient had been considered a "delicate child." She had had the usual childhood diseases, including mumps, scarlet fever and diphtheria. She had had an appendectomy and a uterine suspension at the age of 29 and a tonsillectomy and adenoidectomy at the age of 37. A lipoma had been removed from her arm under local anaesthesia when she was at about the age of 67. She had had occasional attacks of malaria during early adult life but had had none for many years. Constipation had been a problem for years, relieved by laxatives.

Menstrual periods had begun at 14 years and had always been regular and normal. The patient had had a natural menopause at 50 without notable climacteric disturbance. There had been no pregnancies.

This patient had had arthritis in her right hip, knee and ankle since the age of 45. In 1946, when she was 67, this had become worse and the left knee and both wrists and fingers began to pain. Pronounced arthritic deformities developed. The patient felt generally ill and lost weight rapidly, going from 125 to 87 pounds (57 to 40 Kg.).

At that time laboratory study under direction of Dr. Helen J. Snook, Oakland, Calif., showed mild anemia with a normal color index. A leukocyte count was 5,550, with a high percentage of polymorphonuclear cells. The blood sedimentation rate was rapid. Results of urinalysis were normal. The basal metabolic rate was + 12.

The patient had improved under treatment for a time, but late in 1948 both her mouth and eye symptoms and her arthritis had become worse, and she had been bedfast since. Early in 1949 her blood count was essentially as noted above and the sedimentation rate was again rapid.

Her general condition slowly deteriorated until in March 1950 she was admitted to the University of California Hospital under the care of Dr. Gilbert Gordon. At that time her weight was down to 64 pounds (29 Kg.), swallowing had become so difficult that she could scarcely take fluids orally and fluids were given parenterally to restore hydration. Treatment with testosterone propionate was begun intramuscularly in doses of 10 mg. three times weekly. After this, improvement in the mucous membranes of the eyes and mouth occurred rapidly. Within 48 hours there was less photophobia and an increase in tears (from almost none) as measured by the Schirmer test. Within a week the improvement was appreciable and Schirmer's test showed a moistening of the filter paper to 15 mm. in five minutes.

The dysphagia became less pronounced. There was no improvement in the arthritis, however, until about three weeks later, when treatment with desoxycorticosterone acetate, 5 mg., and ascorbic acid, 1.0 Gm., was begun intramuscularly. This gave pronounced relief from joint pain and enabled greater joint motion. Her general condition also improved rapidly, and when she left the hospital after 7½ weeks her weight was up to 80 pounds (36 Kg.). She was able to eat a regular diet without trouble. She has now been home about seven weeks. She is taking methyl testosterone linguets® orally, 5 mg. dissolved beneath the tongue daily, and receiving the desoxycorticosterone acetate and ascorbic acid intramuscularly every four or five days with continued improvement in her eye, mouth and joint symptoms.

COMMENT

In brief review, all five of these cases showed long-standing dryness of both mouth and eyes. All five patients were women. In all but one the symptoms first appeared at the time of, or after, the menopause. In one, ill defined eye symptoms appeared earlier but the mouth and eye symptoms became manifest at about the time of the climacteric. In none was there any evident local lesion causing destruction of the salivary or lacrimal glands or any organic lesion of the nervous system to interfere with its function.

In four cases there were associated signs of foci of infection. In four arthritis was a problem during at least part of the time, and there was a tendency toward anemia in the same number. In three emotional disturbance or tension were noted as associated factors. In two there was coincident severe systemic disease.

TREATMENT

The method of treatment of mouth dryness due to salivary deficiency depends, of course, on the cause, if one can be determined. If the condition is associated with dehydration or some acute systemic disease, for example, it can be expected to disappear when the basic disease clears. If it accompanies diabetes it should improve as the diabetes is brought under control. Faber [5] reported that the mouth dryness and atrophy associated with pernicious anemia and iron deficiency anemia tend to clear when the blood picture improves under appropriate treatment.

In the idiopathic cases of mouth dryness or Sjögren's syndrome treatment is usually unsatisfactory except for palliation. Pilocarpine has been advocated and used since the days of Hutchinson [18] and Hadden.[20b] As previously noted, Furstenberg and Crosby [3] discussed the use of pilocarpine in a particular group of patients with success. Physostigmine may also be used similarly.

Vitamin and endocrine treatments have apparently rarely been helpful.

Friedman and Gernand [57] reported satisfactory control of Sjögren's syndrome with diethylstilbestrol. Fried and Goldzieher [58] used diethyl-

58. Fried, J. J., and Goldzieher, M. A.: The Endocrine Treatment of Keratoconjunctivitis Sicca, Am. J. Ophth. **27**:1003 (Sept.) 1944.

stilbestrol and progesterone together satisfactorily. Estrogenic hormone therapy was unsuccessful in three of my patients, as it was in Behrman and Lee's [52] case and others. One of the patients reported here was perhaps benefited by treatment with testosterone.

Surgical treatment of Sjögren's syndrome by removal of the superior cervical ganglion was unsuccessful in a case reported by Critchley and Meadows.[59] Leriche,[60] on the other hand, reported some improvement following a somewhat similar operation. There were some annoying side reactions. The effect of procaine (novocain®) block in this area should first be tried. Leriche stressed the need for doing this operation early, before advanced atrophy of the lacrimal and salivary glands has occurred.

I noted no mention of any careful attempt at psychotherapy for this problem. There is ample evidence to suggest that analysis and treatment by this method should be considered in selected cases.

SUMMARY AND CONCLUSIONS

Dry mouth is a disturbance due to many different causes. Alone it is distressing and may cause severe local changes but does not preclude reasonably good general health.

The anatomy and physiology of the salivary glands are complicated, and salivary function is sensitive to changes occurring in many, if not all, of the systems of the body.

Inadequate amounts of saliva and mouth dryness may result from such causes as congenital hypoplasia or absence of the salivary glands; loss of gland substance due to surgical operation, roentgen ray or radium damage or infiltration by specific disease, or inadequate secretory stimulation due to organic lesions of the nervous system, chemical disturbances in conduction or reception of nerve impulses and the effect of drugs or toxic agents.

Temporary dryness of the mouth may result from mouth breathing, excessive speaking and normal emotional reactions.

There is both clinical and experimental evidence that abnormal emotional states, neuropsychiatric disorders and psychoses may cause prolonged salivary suppression.

Salivary secretion is lessened by dehydration, and dry mouth may occur as a symptom in acute febrile diseases, diabetes mellitus and insipidus and other systemic diseases.

Idiopathic dryness of the mouth and dryness of the eyes (kerato-conjunctivitis sicca) commonly occur together. Dryness of the mucous

59. Critchley, M., and Meadows, S. P.: Xerostomia and Xerophthalmia, Proc. Roy. Soc. Med. **26**:308 (Jan.) 1933.

60. Leriche, R.: Traitement chirurgical du syndrome de Sjögren (œil sec et bouche sèche): Résultat au bout de ving-huit mois d'une double section du nerf vertébral; Nature de la maladie, Presse méd. **55**:77 (Feb. 1) 1947.

membranes of the nose, throat and vagina and deficient stomach secretion may also be present. Such cases are often considered as examples of a syndrome usually designated as Sjögren's syndrome or the sicca syndrome.

There are similarities between many of the features of this syndrome and the changes seen in deficiencies of vitamin A, nicotinic acid and riboflavin and in pernicious anemia, iron deficiency anemia and the Plummer-Vinson syndrome.

The frequent coincidence of chronic rheumatoid arthritis, dry mouth and keratoconjunctivitis sicca is especially noteworthy. Rapid blood sedimentation rate, relative lymphocytosis and focal infection are common associated observations.

The sicca syndrome occurs most frequently in postmenopausal women. This and hormone titration experiments indicate that hormonal insufficiency may be etiologically important.

It seems probable that varying combinations of the above disturbances result at times in inhibition of salivary and lacrimal secretions while an otherwise normally functioning human organism can adequately compensate for one or a few of them. As the varying etiological factors involved in this syndrome are better understood individual cases may, perhaps, be more accurately classified.

ABSTRACT OF DISCUSSION

Dr. George M. Lewis, New York: At best, dryness of the mouth is an uncomfortable sensation. It may be physiological, temporary and the normal response to an emotional situation. If exaggerated and if part of a syndrome involving other glands of secretion, the condition may be of serious import. Dr. Allington's monograph should be read in full for appreciation of all the various etiological factors which can be involved and the clinical patterns that may develop. He has wisely stressed the more important ones. The symptom of dryness of the mouth is a not uncommon complaint of patients who have taken antihistamine drugs, as may be observed, particularly if these persons are questioned directly. Fortunately, the complaint usually is mild and often transient and may be relieved by chewing gum or by the retention in the mouth of a demulcent lozenge.

It has been my experience that burning tongue is a very frequent accompaniment. In all patients with this complaint it is important to rule out by history, physical examination and laboratory tests the presence of pernicious anemia, diabetes and thyroid disease. It would seem that psychosomatic factors will prove to be important in a large number of patients.

In Sjögren's syndrome, dryness of the mouth is an important although often overlooked or discounted symptom. The fact that 40 per cent of patients with rheumatoid arthritis show evidence of the sicca syndrome would indicate a rather close association between the two disorders.

In closing, would Dr. Allington summarize the data in his series of five cases? I think they are extremely interesting, and he could probably quickly give us just the main details of these cases. He has had a very unusual opportunity in being able to observe that many instances of Sjögren's syndrome, and I take it from what he said that he believes that plain dryness, idiopathic dryness of the mouth in the

absence of any known cause, is a forme fruste of this syndrome. He might comment on whether I am correct in assuming that from what he said.

I think also we should appreciate any comment he would care to give on the therapy of the idiopathic type of dry mouth because in the few cases that I have had experience with I have had very little success in treatment with any known method. I think occasionally some psychosomatic approach may be helpful, but these cases constitute a rather difficult group in which to obtain permanent therapeutic results.

Dr. Everett S. Lain, Oklahoma City: I very much enjoyed this presentation by Dr. Allington. Dryness of the mouth is a symptom that is very commonly encountered if we go into the history of the patients who have had various disorders of the mouth. They don't always mention this excessive dryness because this symptom in many cases is temporary. Often, however, the cases are lasting. Dr. Allington mentioned one particular type of case in which the etiology is confusing and complicated. Therefore I feel this condition, namely, that due to the formation of calculi in the glandular ducts, needs more emphasis. It has been my experience to see two cases which were unilateral. Eventually the calculi were removed, after which operation the dryness of the mouth disappeared.

In one case there was extreme dryness of the mouth. I had seen the patient occasionally for several months. Eventually the development of a sublingual tumor on one side called my attention to the need of a roentgenogram, which disclosed a large calculus. I think that calculi in the glandular ducts should always be kept in mind as a possible cause in any persistent case of dryness of the mouth.

Dr. Norman N. Epstein, San Francisco: I also had the opportunity to read Dr. Allington's paper, and his short verbal presentation could hardly do justice to the thoroughly excellent piece of work that he has done. I certainly urge that you read it in full. He first called attention to Sjögren's syndrome in 1947 by presenting a patient showing these symptoms before a combined meeting of the San Francisco, Los Angeles and Pacific Northwest Dermatologic Societies.[56]

I was particularly interested in Dr. Allington's discussion of this syndrome, although he goes into great detail with regard to all the causes and possible etiologic factors which may produce dryness of the mouth. Sjögren's syndrome includes a set of symptoms which represent some constitutional disease. Dryness of the mouth is one symptom while dryness of the eyes and arthritis and possibly other symptoms are present. The occurrence of this syndrome in women after the menopause suggests possibly a hormonal disturbance.

Dr. Allington did not present the case histories because of the lack of time, but in one case he stated that therapy with diethylstilbestrol and progesterone and also desoxycorticosterone acetate with ascorbic acid apparently did relieve the condition. Desoxycorticosterone acetate, known by the trade name of doca,® has been used for the treatment of arthritis as a substitute for ACTH and cortisone. The experience at the University of California has not been very dramatic with this substance. Perhaps ACTH or cortisone will be of value in Sjögren's syndrome. It is also probable that this syndrome is commoner than we are aware of its being, as perhaps many of us do not look for this triad of symptoms.

Dr. Harry L. Arnold, Jr., Honolulu, Hawaii: May I ask whether the dryness of the mouth was related at all to the taking of morphine or morphine with atropine in advanced cases of arthritis?

Dr. Stephen Rothman, Chicago: Acetylcholine being the natural chemical mediator of nerve impulses to the salivary glands, one of the stable choline esters or neostigmine (prostigmin®) should be tried in each case. Of course, if the dryness is based on atrophy of the glands this type of treatment will be ineffective.

DR. HERMAN V. ALLINGTON, Oakland, Calif.: I should like to thank the discussants. In answer to Dr. Lewis all my five patients were women. In all except one of them the trouble first appeared after the menopause. One had minor symptoms prior to this. Four of them have had some degree of arthritis.

Four showed signs of foci of infection and varying degrees of anemia or had past history of anemia. In three there were definite signs of emotional disturbance. One had had a "nervous breakdown" in early adult life and had been later diagnosed as having "nervous exhaustion." One patient had extremely severe rheumatoid arthritis accompanied by pronounced general debility. In one there was a rapidly progressive hepatic cirrhosis leading to the patient's death.

It was in the patient with severe rheumatoid arthritis that Dr. Epstein mentioned improvement occurring after the administration of testosterone and of desoxycorticosterone acetate and ascorbic acid. The improvement first began in the mouth and eye changes during the time the patient was receiving general supportive care and testosterone. The improvement in the arthritis did not begin until after the desoxycorticosterone acetate and ascorbic acid were given. This observation would tend to indicate that it was the testosterone that helped the symptoms of Sjögren's syndrome.

One other case has been reported as having been controlled by the administration of testosterone. Several have been reported as having been helped by estrogen and one by estrogen and progesterone. In many of the failures with endocrine therapy, including some of my own cases, I believe that the treatment has not been well controlled. These cases should be studied by all available means by one who is expert in endocrinology.

In answer to Dr. Rothman, physostigmine has been reported as helpful. I do not know whether it has any advantage over pilocarpine in this syndrome. Drs. Furstenberg and Crosby from the University of Michigan reported that in some cases the effect of pilocarpine can be enhanced by keeping the patient in a state of mild acidosis by reducing alkaline intake and administration of ammonium chloride.

Dr. Lewis, I believe that the mouth and eye symptoms are equally a part of the sicca syndrome. In some cases the mouth is involved first and most severely, and in some the eye symptoms are paramount.

Dr. Arnold, I know that morphine and its derivatives do suppress salivary gland function. Morphine could not have been the cause in any of my cases, however.

MACROCYTIC ANEMIA AND IMPAIRED LIVER FUNCTION IN ECZEMATOUS AND CERTAIN OTHER DERMATOSES

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THE PATIENT with a skin disorder who expresses the belief that something "may be lacking" in his system deserves to be taken seriously. Profound nutritional disturbances may exist and may be the cause of certain obscure dermatoses even in the absence of obvious dietary deficiencies or characteristic clinical manifestations. In this brief discussion attention will be focused on two nutritional and metabolic disturbances which have recently been discussed in dermatological literature and several illustrative cases in our experience will be described.

MACROCYTIC NUTRITIONAL ANEMIA

Stryker and Halbeisen [1] in 1945 called to the attention of dermatologists a relationship between certain dermatoses and nutritional disorders as revealed by a macrocytic anemia. They carried out hematological studies on 179 patients presenting various dermatoses, with a view to determining the presence of a macrocytic anemia. It was pointed out that a routine blood examination including red cell count, white cell count and hemoglobin and color index determinations may fail completely to detect the presence of a macrocytic anemia of nutritional origin caused by a deficiency in one or more of the vitamin B complex factors. Only by measuring the mean corpuscular volume and the mean corpuscular hemoglobin concentration, a very simple calculation based on the packed cell volume as demonstrated by Wintrobe,[2] can this important nutritional disturbance be detected.

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 21, 1950.

1. Stryker, G. V., and Halbeisen, W. A.: Determination of Macrocytic Anemia as an Aid in Diagnosis of Certain Deficiency Dermatoses, Arch. Dermat. & Syph. **51**:116-123 (Feb.) 1945.

2. Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocyte: Methods of Determination and Clinical Application, J. Lab. & Clin. Med. **17**:899-912 (Jan.) 1932.

Forty-two of the 179 patients studied presented lesions which did not conform to any dermatological entity. Over half of this group was found by hematological studies to have a macrocytic anemia probably due to vitamin B deficiency, and both the clinical and the blood picture responded promptly as the result of intramuscular injections of crude liver extract. The eruption in these cases involved especially the sides of the neck, the face, the anterior part of the shoulders, the upper part of the chest and the areas immediately adjacent to the anterior axillary folds. The lesions were patchy or diffuse, erythematous, itchy, dry, scaly or vesicular and in long-standing cases somewhat thickened. In some instances they resembled contact dermatitis.

Gross [3] has for a number of years insisted on the value of crude liver extract administered intramuscularly in a variety of dermatological conditions which he stated the belief were due to a deficiency of the vitamin B complex, on the basis of history and other clinical features. Gross did not utilize the blood picture to confirm the diagnosis of a vitamin deficiency. He expressed the opinion that dietary deficiencies were to blame in only occasional instances and that constitutional defects resulting in a failure to utilize vitamins were frequently at fault. He included seborrheic eruptions, extensive moniliasis and vulvar and anal eczema, among other conditions, in the cases studied.

According to Bortz and Haden [4] and others, macrocytic anemia or macrocytosis may develop when the erythrocyte-maturing factor (EMF) is lacking either through dietary deficiency or because of faulty absorption, utilization or storage of this important element. The erythrocyte-maturing factor depends on the interaction of the intrinsic factor supplied by the gastric glands and the extrinsic factor supplied by the diet. Pernicious anemia and sprue are two types of macrocytic anemia. Liver disease, including cirrhosis, may cause macrocytosis through faulty utilization and storage of the erythrocyte-maturing factor.

Gastric acidity may be, but is not necessarily, deficient in macrocytic nutritional anemia. Kemp [5] reported a series of 15 cases in male vegetarians living in India, in all of whom free gastric hydrochloric acid was present. Three of these persons treated with folic acid given orally had a much more rapid response than the other 12, who were treated with crude liver extract administered intragluteally and iron given by mouth.

It is not within the scope of this paper to enter into a lengthy discussion of the various types of macrocytic anemia. It may be said in

3. Cross, P.: Nonpellagrous Eruptions Due to Deficiency of Vitamin B Complex, Arch. Dermat. & Syph. **43**:504-531 (March) 1941.

4. Bortz, D. W., and Haden, R. L.: Diagnosis and Treatment of Macrocytosis, Cleveland Clin. Quart. **16**:8-11 (Jan.) 1949.

5. Kemp, T. A.: Liver and Folic Acid in the Treatment of Nutritional Macrocytic Anaemia: Comparison of Results, Lancet **2**:350-353 (Sept. 6) 1947.

general that pernicious anemia is characterized by a mean corpuscular hemoglobin concentration of 32 per cent or more,[6] whereas macrocytic nutritional anemia tends to have a concentration below 30 per cent. Pernicious anemia is also characterized by achlorhydria and frequently by neurological changes.

Wintrobe stated that the normal mean corpuscular volume varies between 80 and 94 cubic microns, with values above 94 constituting a condition of macrocytosis. The normal range of mean corpuscular hemoglobin concentration is between 33 and 38 per cent. In Stryker and Halbeisen's series of cases there was a tendency for the mean corpuscular volume to exceed 100 cubic microns, a figure of 142 being recorded in one case. At the same time, the mean corpuscular hemoglobin concentration was usually below 32 per cent and in one case was as low as 21 per cent, an abnormally large erythrocyte with a comparatively low concentration of hemoglobin thus being indicated. After the intramuscular injection of crude liver extract there was a pronounced clinical improvement or cure associated with improvement in the blood picture, including a drop in the mean corpuscular volume and a rise in the mean corpuscular hemoglobin concentration. It should again be emphasized that observations of the red cell count, amount of hemoglobin and color index alone are wholly inadequate in detecting this nutritional type of anemia, since in some instances these figures may not be unduly abnormal.

During the past two years we have encountered 27 patients with inflammatory dermatoses of obscure origin in whom the picture of macrocytic anemia was found, sometimes suggested by the history, the general appearance or the presence of a smooth red tongue, among other indications. Both the skin lesions and the blood picture have shown gratifying responses to the intragluteal injections of crude liver extract containing folic acid together with high potency vitamin B complex and iron administered orally and, more recently, to intragluteal injections of vitamin B_{12}.

Of these 27 patients 21 were female and 6 male. The majority were in the middle or older age group, although eight were below the age of 40. The eruption in most cases was eczematous, usually of a rather nondescript type. The face, neck, chest, scalp and arms were the areas most commonly involved, although in some cases the eruption was widely disseminated. There was one case of acne urticata and one case of "purpuric dermatitis of the legs." Liver function tests were done on eight of these patients, and in each case a mild to severe disturbance in liver function was revealed by dye retention in the sulfobromophthalein test. Further studies will be carried out on the possible relationship between macrocytic anemia and disturbed liver function.

6. Cecil, R. L.; McDermott, W., and Wolff, H. G.: A Textbook of Medicine, ed. 7, Philadelphia, W. B. Saunders Company, 1947, p. 1094.

TABLE 1.—*Observations Concerning Patients Showing Evidence of Macrocytic Anemia by the Method of Wintrobe (Mean Corpuscular Volume Above Ninety-Five Cubic Microns Abnormal)*

Case	Sex, Age	Diagnosis and Duration of Condition	Mean Corpuscular Volume, Cubic Microns		Mean Corpuscular Hemoglobin Concentration, Per Cent		Treatment	Result	Remarks
			Before Treatment	After Treatment	Before Treatment	After Treatment			
M. E. W.	F, 70	Eczema of face, neck, chest; 1½ yr.	98.8	86.9	29.4	30.8	Liver extract, vitamins and iron	Cure	.....
M. S.	F, 40	Seborrheic dermatitis, scalp; 2 yr.	102.0	....	28.9	....	Liver extract, vitamins and iron	Improvement	.....
P. R.	F, 28	Eczema, neck and chest; 10 mo.	102.5	....	29.2	....	Liver extract, vitamins and iron	Improvement	.....
M. R.	F, 45	Eczema of scalp, face, neck and crotch; 2 yr.	103.9	85.6	30.3	32.5	Liver extract, vitamins and iron	Cure	Remarkable improvement in two months
A. N.	F, 65	Eczema of face, neck and crotch; several years	103.7	80.3	28.6	35.5	Liver extract, vitamins and iron	Cure	.....
M. M.	F, 30	Acne urticata; 6-7 yr.	99.2	....	28.3	....	Liver extract, vitamins and iron	Much improvement	.....
H. L.	F, 55	Dermatitis venenata of feet, sore tongue; 3 wk.	99.7	....	30.4	....	Liver extract, vitamins and iron	Cure	Patient sensitive to shoe leather
M. H.	F, 30	Eczema of face, scalp, flexural area; 18 mo.	101.8	81.5	29.5	34.8	Liver extract, vitamins and iron	Improvement	Patient sensitive to local medication
P. G.	F, 36	Eczema, suboccipital and flexural area; 1½ yr.	111.2	97.8	27.5	30.1	Liver extract, vitamins and iron	Much improvement	.....
M. F.	F, 66	Eczema of face, arms and thighs; 5 yr.	100.00	....	30.5	....	Liver extract, vitamins, iron and methischol *	No improvement	Defective liver function
N. D.	F, 74	Eczema of face; 2 mo.	103.5	....	30.4	....	Liver extract, vitamins and iron	Cure	.....
N. D. (Recurrence 1 yr. later)	F, 75	Dermatitis of face and eyelids; 2 wk.	96.8	87.4	28.6	31.7	Vitamin B_{12} intragluteally	Cure	Second blood count 17 days after first
N. C.	F, 77	Pruritus vulvae et ani; 5 mo.	100.6	86.0	28.7	32.1	Liver extract, vitamins and iron	Improvement	Irregular visits with relapses
S. B.	F, 45	Eczema of hands and forearms; 3 mo.	97.0	....	27.4	....	Patient did not continue under treatment	.....	.....

G. B.	M, 63	Eczema of neck, hands, back, etc.; 6 wk.	106.5	....	28.5	....	Liver extract, vitamins and iron	Improvement	.....
F. M. C.	M, 37	Purpuric dermatitis of legs; 6-8 mo.	97.2	85.8	31.5	33.3	Liver extract, vitamins, iron and methischol *	Much improvement	Also mildly defective liver function
J. M. B.	M, 70	Eczema, widespread; 4 wk.	98.7	....	31.1	....	Liver extract, vitamins and methischol *	Much improvement	Severely defective liver function
I. H.	F, 50	Eczema, widespread; 4 mo.	97.1	....	31.1	....	Liver extract, vitamins, iron and methischol *	Much improvement	Also mildly defective liver function
C. M.	M, 68	Pruritus, generalized; 2 wk.	95.8	....	31.1	....	Liver extract, vitamins and methischol *	Cure	Also moderately severe defective liver function
J. M.	F, 34	Eczema, widespread ("nummular"); 3 yr.	95.6	....	30.1	....	Liver extract, vitamins, iron and methischol *	Much improvement	Moderately defective liver function
D. M.	F, 72	Eczema of legs, widespread; 1½ yr.	101.1	91.1	28.7	30.7	Liver extract, vitamins, iron and methischol *	Much improvement	Also mildly defective liver function
C. E.	F, 85+	Eczema, dorsum of feet and ankles; several years	112.5	88.7	29.8	30.9	Iron and vitamins	Patient not seen again	.....
R. C.	F, 85	"Eczema," nondescript; 20 yr.	100.3	97.0	33.3	30.2	Liver extract, vitamins and iron	Cure in one month	.....
R. M. G.	M, 70±	"Eczema," nondescript; 4 mo.	105.6	92.4	29.2	31.0	Vitamin B_{12}	Cure in three months	.....
H. H.	F, 25	Hidrosadenitis suppurativa of axillas; acne conglobata(?) thighs; 5 yr.	99.7	....	29.7	....	Iron, vitamins, folic acid and liver extract	Little improvement	.....
A. M.	F, 51	Lupus erythematosus, discoid after gold therapy	96.4	84.1	28.7	32.1	Liver extract, iron and vitamins	Lupus erythematosus remained inactive	.....
V. P.	F, 39	Eczema; 6 yr. (contact dermatitis?)	98.3	94.4	28.2	29.5	Vitamin B_{12}	Near cure after one month	.....
S. A. L.	M, 68	"Eczema," face and legs	97.4	....	31.5	....	Vitamin B_{12}	Pronounced improvement	Patient also had disturbed liver function

* Registered trademark.

Sturgis [7] expressed the opinion that in any case of macrocytic anemia in which there is free hydrochloric acid, an absence of acroparesthesia and other signs of neural involvement one should always consider the possibility that the patient has extensive involvement of the liver, most commonly cirrhosis, and liver function tests should be done.

Treatment consisted in the intragluteal administration of 2 cc. of crude liver extract (2 U. S. P. units per cubic centimeter), containing 2 mg. of folic acid per cubic centimeter. Injections were given at intervals of five to seven days. In addition, a preparation of the vitamin B complex derived from yeast and liver with added folic acid and iron was administered by mouth. Various other therapeutic procedures, such as the oral administration of ascorbic acid and antihistamine drugs and the uses of ointments, lotions, compresses and roentgen therapy locally and occasionally calcium intravenously or hapamine® (a chemical combination of histamine and despeciated horse serum globulin) subcutaneously.

From the standpoint of one wishing to make a scientific appraisal of the value of specific therapy for the anemia in relieving the dermatoses, the use of these accessory therapeutic procedures might be criticized. Yet in the private practice of medicine one is obligated to utilize whatever procedures experience has taught will bring about the quickest relief. There is little doubt of the value of treatment directed toward the vitamin deficiency associated with the macrocytic anemia in view of the gratifying response in nearly all cases. In 14 cases the blood count was repeated from one to several months after the beginning of treatment, and in each case there was improvement not only in the red cell count and amount of hemoglobin but especially in the macrocytic picture. In all cases there was a drop in the mean corpuscular volume and an increase in the mean corpuscular hemoglobin concentration. These changes coincided with a disappearance or improvement of the eruption.

Vitamin B_{12} was not available during the early part of these studies. During recent months, vitamin B_{12} administered intragluteally in a dose of 10 to 15 micrograms once a week has given strikingly beneficial results.

The following case may be cited as a good example of a chronic and recurrent eczematous dermatitis containing both allergic and probably psychosomatic elements which presented a typical blood picture of a macrocytic anemia and which responded promptly both dermatologically and hematologically to treatment as indicated above.

CASE 1.—M. R., a white woman aged 46 employed in a responsible position by the State Board of Education, had had an eczematous dermatitis at intervals since the age of 20, with lesions occurring chiefly on the face, neck and scalp and more

7. Sturgis, C. C.: Hematology, Springfield, Ill., Charles C Thomas, Publisher, 1948, p. 262.

recently in the axillary, pubic and crural regions. The lesions when examined on March 3, 1948, had been acute for three months and were symmetrical, erythematous, scaly and excoriated, with some exudation in the pubic area. Local treatment consisted in the application of boric acid compresses and 10 per cent boric acid ointment in a water-absorbing base. Systemic therapy consisted in the administration of crude liver extract with folic acid, 2 cc., intragluteally at approximately weekly intervals, also hapamine® subcutaneously, calcium intravenously and the vitamin B complex, tripelennamine (pyribenzamine®), ascorbic acid and iron orally.

Fig. 1.—Patient M. R. Eczematous eruption associated with macrocytic nutritional anemia. Appearance of eruption at time of the patient's blood count.

Improvement was rapid; within nine weeks the face was essentially healed although there were a few scattered lesions on the neck and trunk. The photographs taken nine weeks apart illustrate the degree of clinical improvement. The contrast of the two blood counts taken nine weeks apart was equally striking: the red cell count rose from 3,800,000 to 4,680,000; the hemoglobin from 12 Gm., or 78 per cent, to 13 Gm., or 84 per cent; the mean corpuscular volume dropped from 103.9 to 85 cubic microns, and the mean corpuscular hemoglobin concentration rose from 30.0 to 32.5 per cent.

This patient has been observed at intervals during the ensuing two years. She has taken her medication intermittently and has remained essentially well. Repeated blood counts since the original one have never exhibited macrocytosis.

The case is one of many in which clinical improvement of skin lesions has paralleled hematological improvement. In this particular case, even though the hapamine,® calcium, ascorbic acid and tripelennamine may have contributed to the immediate improvement of the dermatosis, they could not have affected the blood picture and it was probably the improvement of the patient's general nutrition which produced a general

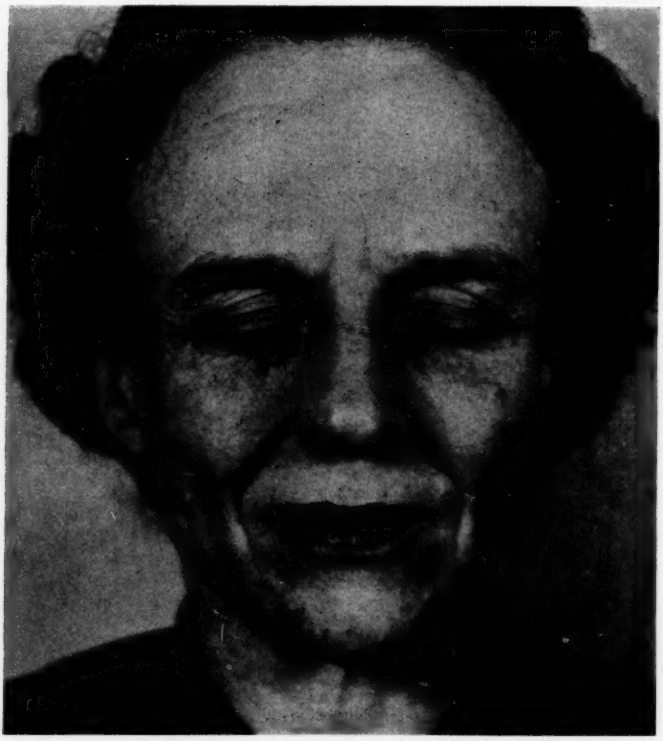

Fig. 2.—Appearance of patient shown in figure 1 nine weeks after the beginning of therapy with crude liver extract and folic acid.

improvement in her physical well-being and a long-lasting improvement in her skin condition.

DISTURBANCES IN LIVER FUNCTION

A most stimulating paper, published over a year ago by Eichenlaub and Osbourn,[8] on the role of disturbed liver function in the causation

8. Eichenlaub, F. J., and Osbourn, R. A.: Role of the Liver in Congestive Eczema, Arch. Dermat. & Syph. **57**:171-177 (Feb.) 1948.

of certain types of eczematous dermatoses arouses our interest in this subject. These authors reviewed previous reports and discussed the various types of functions performed by the liver and the types of liver function tests. It is probably true that no single test can reveal all the various disturbed functions of the liver, but the sulfobromophthalein test is generally regarded as providing a fairly reliable index of liver damage.

According to Mateer and co-workers,[9] the test is probably the most valuable single test available for evaluating cases of chronic hepatitis, hepatic cirrhosis and metastatic carcinoma of the liver. If the photoelectric method is used the test can be employed even in the presence of jaundice.

Bruger and Oppenheim[10] expressed agreement that the sulfobromophthalein test has won the widest acceptance among dye tests and has the advantages of sensitiveness, safety and simplicity. The dye is removed from the blood stream by the Kupffer cells of the liver and then excreted by the parenchymal cells into the bile. It reveals the presence of chronic parenchymal damage. The cephalin-cholesterol flocculation and thymol turbidity tests are considered by these authors to be more appropriate in cases of acute parenchymal damage.

The test is performed by means of the intravenous injection of the dye in a dose of 5 mg. per kilogram of body weight and then determination of the percentage of the dye retained in the circulating blood (i. e., not taken up by the liver) at the end of 30 and 45 minutes. In normally functioning livers 5 to 7 per cent of the dye is found in the 30 minute sample of blood, and none should be found at 45 minutes when the comparator block method is used, as in our studies. When the photoelectric method is used the observation of any dye above 4 per cent at the end of 45 minutes is abnormal.

Eichenlaub and Osbourn reported a series of eight cases of what they described as "congestive eczema" with lesions occurring on the legs, arms and other areas. In all these cases there was abnormal retention of sulfobromophthalein in contrast to a control group of eight patients who presented other types of dermatoses. Treatment consisted in the intramuscular injection of crude liver extract, use of a diet high in protein and carbohydrate and low in fat, large doses of the vitamin B complex given by mouth and supplemental feeding of protein hydrolysates, resulting in either complete disappearance of or definite improvement in the dermatosis.

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9. Mateer, J. G., and Others: Chronic Subclinical Impairment of the Liver: Early Diagnosis and Treatment; Further Improvement and Evaluation of Certain Liver Function Tests, J. A. M. A. **133**:909-916 (March 29) 1947.

10. Bruger, M., and Oppenheim, E.: The Present Status of Liver Function Tests Including Observations on the Newer Flocculation Procedures, Bull. New York Acad. Med. **25**:16-31 (Jan.) 1949.

Guy, Jacob and Guy [11] discussed the problem of geriatric nutritional eczema with lesions involving the legs or more widespread areas from the point of view of hypoproteinemia and suggested that anemia and hepatic diseases were among the causative factors. No mention was made of macrocytosis or of liver function studies, but gratifying results were obtained from treatment which included a diet rich in proteins, the administration of vitamins from yeast and liver and correction of anemia.

The stimulus of this work has prompted us to carry out sulfobromophthalein liver function tests on some of our patients presenting obscure inflammatory and pruritic dermatoses with the result that a number of long-standing and recalcitrant cases have finally been brought under control.

A history of the moderate daily to excessive consumption of alcohol, restricted diet, residence in the tropics, jaundice and malaria, among other factors, often suggests the possibility of liver damage.

During the past two years 85 patients with various dermatoses have been observed who have been found to have disturbed liver function as revealed by the sulfobromophthalein dye test, using the comparator block method. In addition, three patients were seen who were under the care of internists for liver damage, for whom other types of liver function tests had substantiated the diagnosis.

The dermatoses included nondescript eczematous eruptions, many of which were widespread and had a strong tendency to involve flexural areas (ears, axilla, crotch and intergluteal region). There were two cases of long-standing pruritic and vesicular eruptions of the palms with occasional eruptions elsewhere. There were two cases of severe acne rosacea of the non-Demodex type in middle-aged men, both of whom were heavy consumers of alcohol. A recent paper on the relationship of acne rosacea to disturbed liver function was read at the 1950 meeting of the California Medical Association in San Diego by Robert O. Lofgren,[12] who reported impaired liver function in a series of eight out of nine cases.

In addition to the above-mentioned disorders, chronic urticaria, hyperkeratotic dermatitis of the hands, psoriasis, seborrheic dermatitis, "nummular" eczema, persistent nonvaricose eczema of the legs, acne urticata, "purpuric dermatitis" of the legs and localized neurodermatitis were among the diagnoses most frequently encountered. Two cases in middle-aged men began with ill defined, diffuse, persistent, erythema-

11. Guy, W. H.; Jacob, F. M., and Guy, W. B.: Geriatric Nutritional Eczema, Arch. Dermat. & Syph. **57**:822-827 (May) 1948.

12. Lofgren, R. O.: Rosacea in Relation to Liver Malfunction and Estrogen Metabolism, read at the Seventy-Ninth Annual Session of the California Medical Association, San Diego, Calif., May 1, 1950.

tous eruptions on the face suggestive of contact dermatitis from shaving cosmetics, with the later development of nondescript eczematous eruptions elsewhere suggesting the "nummular" type. Two patients presented widespread pruritus with excoriations which at times resembled pruritus hiemalis and at other times were reminiscent of pediculosis.

Of the 87 patients, 61 were male and 26 female. The ages were for the most part above 50, there being 57 patients above the age of 50 and only 10 below the age of 40. A history of the use of alcohol was noted in 54 cases, in 32, or 37 per cent, of which the patients used alcohol in amounts ranging from daily to heavy.

Some of the test results might be considered borderline, such as those showing a retention of 4 per cent dye at 45 minutes, and yet the best authorities have contended that there should be no dye remaining at 45 minutes when the ordinary colorimeter method is used, as it was in this series. Of the 85 patients on whom sulfobromophthalein tests were done, 15, or 17 per cent of the total, showed seriously damaged livers with a dye retention of as much as 16 per cent at the end of 45 minutes.

According to Rowntree,[13]

> The exact relation of alcohol to the pathogenesis of cirrhosis is not clearly defined. Alcohol may predispose to cirrhosis, may induce malnutrition, engender deficiency syndrome, or it may exert a direct toxic effect. One, or all, may be involved, and they all should be thoroughly investigated as to their role.

Treatment followed the general principles currently advocated for the management of cirrhosis, including avoidance of alcohol; a diet high in protein and carbohydrate and low in fat; the administration of lipotropic substances[14] in the form of choline or methischol,* which contains methionine, inositol and choline, 2 capsules three times daily; administration of high potency vitamin B complex with vitamin C; crude liver extract with folic acid given intragluteally in a dose of 2 cc. at five to seven day intervals, and whatever symptomatic procedures seemed indicated in the individual case.

Response of the skin condition to the above regimen was highly gratifying in many cases. Complete relief or pronounced improvement was achieved for an appreciable number of patients, and satisfactory results were obtained with the great majority of those who remained under treatment for as long as three or four weeks or more. Recurrence of the dermatosis may be anticipated in a fair percentage of cases of liver damage inasmuch as cirrhosis of the liver is a serious disease. The liver possesses remarkable powers of regeneration under appropriate treatment, but the amount of regeneration depends to a considerable

13. Rowntree, L. G.: Some Comments on Portal Cirrhosis, South. M. J. **42**:282-289 (April) 1949.

14. Steigmann, F.: Efficacy of Lipotropic Substances in Treatment of Cirrhosis of Liver, J. A. M. A., **137**:239-243 (May 15) 1948.

TABLE 2.—*Observations Concerning Patients Showing Defective Liver Function as Revealed by Sulfobromophthalein Test Using Five Milligrams of Dye per Kilogram of Weight Intravenously (Comparator Block Method)*

Case	Sex, Age	Diagnosis and Duration of Condition	Dye Retention, %		Treatment *	Result	Use of Alcohol †	Remarks
			30 Minutes	45 Minutes				
H. E. W.	M, 55	Eczema of palms; 30 yr.	16	8	Liver extract, vitamins and methischol ‡	Improvement	D	Also elevated uric acid
L. T.	F, 69	"Purpuric dermatitis" of legs; 2 yr.	16	6	Liver extract, vitamins, methischol,‡ ascorbic acid and rutin	Much improvement	L	Also positive capillary fragility test result
C. W. S.	M, 60?	Lichenoid purpuric lesions of leg; 7 yr.	20	8	Liver extract, vitamins and methischol ‡	Improvement	L	.....
H. J. S.	M, 57	Psoriasis (?), scalp and elbows; 2 yr.	10	5	Liver extract, vitamins and methischol ‡	Much improvement	H	Also active local therapy
R. E. S.	M, 58	Psoriasis, severe; 33 yr.	20	12	Liver extract, vitamins and methischol ‡	Pronounced improvement	D	"Bathing suit" type of involvement
J. S.	M, 51	Eczema (widespread); 4 yr.	16	16	Patient did not remain under observation	.....	H	Also large lymph node in left groin, 6-8 yr.; lymphoblastoma (?)
J. S.	M	Dermatitis herpetiformis (?); many years	16	12	Liver extract, vitamins and methischol ‡	Improvement	.	Relapse; pronounced improvement following administration of penicillin
W. I. S.	M, 77	Erythroderma; 6 yr., bad for 9 wk.	24	16	Liver extract, vitamins and methischol ‡	Cure	..	Near cure in two months
C. R.	M, 48	Seborrheic dermatitis, acne rosacea; 10 yr.	Other tests showed liver damage		Liver extract and vitamins	Temporary benefit	H	Patient failed to follow diet and continued drinking to excess
B. O. R.	M, 65	Eczema of legs; 5 mo.	20	8	Liver extract, vitamins and methischol ‡	Improvement	O	.....
M. P.	M, 39	Seborrheic dermatitis, acne vulgaris; 9 yr.	8	4	Liver extract, vitamins and methischol ‡	Slight improvement	O	.....
E. G.	F, 69	"Flexural dermatitis"; 8 yr.	20	16	Liver extract, vitamins and methischol ‡	Cure in two months	O	.....
D. S.	F, 36	Neurodermatitis of eyelid and face; 4 yr.	12 8	8 4+	Liver extract, vitamins and methischol ‡	No improvement	I.	Second test two months after first
B. C.	M, 40	Urticaria; 3 mo.	8	4	Liver extract, vitamins and methischol ‡	Cure in three months	M	Patient also received antihistamine drugs
L. B.	F, 66	Flexural dermatitis, face and soles; 6 wk.	16+	4+	Liver extract, vitamins and methischol ‡	Treatment just started	O	.....
D. A.	M, 85	Flexural dermatitis, ears, scalp, etc.; 1 yr.	24	16	Liver extract, vitamins and methischol ‡	Cure	D	.....

D. M.	F, 72	Eczema, legs, face, arms, etc.; 1 mo.—recurrent	12	4	Liver extract, vitamins, iron and methischol ‡	Improvement	O	Patient also had macrocytic anemia
J. M.	F, 34	Eczema (widespread); 3 yr.	12	8+	Liver extract, vitamins, iron and methischol ‡	Much improvement	H	Also slight macrocytic anemia
C. M.	M, 68	Pruritus with excoriations; generalized 2 wk.	16	12	Liver extract, vitamins and methischol ‡	Cure	D	Also slight macrocytic anemia
I. H.	F, 50	Eczema (widespread), scalp, etc.; 4 mo.	8	4	Liver extract, vitamins, iron and methischol ‡	Pronounced iment	H	Also slight macrocytic anemia
J. M. B.	M, 70	Eczema (widespread); 4 wk.	40+	32+	Liver extract, vitamins and methischol ‡	Much improvement; patient discontinued treatment after 12 days	H	Also macrocytic anemia
F. M. C.	M, ..	Purpuric dermatitis of legs, back, arms; 6-8 mo.	8	4	Liver extract, vitamins, methischol,‡ ascorbic acid and rutin	Much improvement	L	Also macrocytic anemia, positive result of capillary fragility test
M. F.	F, 66	Eczema, face, arms, thighs; 5 yr.	20	12	Liver extract, vitamins, iron and methischol ‡	No improvement	O	Also macrocytic anemia
L. O.	M, 45	Seborrheic dermatitis, scalp, axilla and chest; 4-5 yr.	12	8	Liver extract, vitamins and methischol ‡	Improvement	D	.....
W. O.	M, 46	Eczema, hands and feet; 1 mo.	12	4	Liver extract, vitamins and methischol ‡	Cure	MH	.....
T. N.	M, 42	Erythematous and papular dermatitis, face and scalp; 2 yr.	12	4	Liver extract, vitamins and methischol ‡	Much improvement	M	Patient drank 20 cups of coffee with cream daily
G. Z.	M, 43	Eczema, generalized; 6 yr. at intervals	32	32	Liver extract, vitamins and methischol ‡	Cure	H	Patient died later of cirrhosis of the liver
F. J. Y.	M, 59	Eczema, widespread; 2½ mo.	24	20	Liver extract, vitamins and methischol ‡	Cure	O	Patient had lived in tropics, had malaria and was on treatment with quinacrine
F. L.	M, 61	Eczema, hands, ankles, seborrheic dermatitis, scalp; 1 yr.	12	8	Liver extract, vitamins and methischol ‡	Much improvement	H	Patient had been user of alcohol up to six years ago; had had none since
M. L.	F, 54	"Flexural dermatitis" of ears; 2 yr.	16	8	Liver extract, vitamins and methischol ‡	Improvement; patient still under treatment	L	.....

* Treatment in all these cases included a diet high in protein and low in fat, with an abundance of fresh fruit and vegetables, and the avoidance of alcohol.
† The amount of alcohol used is indicated as follows: O, none; M, moderate; L, light; D, daily, and H, heavy.
‡ Registered trademark.

TABLE 2.—*Observations Concerning Patients Showing Defective Liver Function as Revealed by Sulfobromophthalein Test Using Five Milligrams of Dye per Kilogram of Weight Intravenously (Comparator Block Method)—Continued*

Case	Sex, Age	Diagnosis and Duration of Condition	Dye Retention, %		Treatment *	Result	Use of Alcohol †	Remarks
			30 Minutes	45 Minutes				
L. A. K.	F, 74	"Flexural dermatitis"	8	4	Liver extract, vitamins and methischol ‡	Improvement; patient still under treatment	D	.....
F. H.	M, 63	Eczema, widespread; 4 mo.	..	6	Liver extract, vitamins and methischol ‡	Improvement	O	.....
J. H.	M, 54	Eczema, widespread; 6 yr. at intervals	16	12	Liver extract, vitamins and methischol ‡	No improvement; treatment discontinued after three weeks	O	.....
W. G. H.	M, 74	Eczema, widespread; 1½ yr.	16	8	Liver extract, vitamins and methischol ‡	Cure	O	.....
G. Q.	M, 65	Eczema, palms	..	..	Liver extract, vitamins and methischol ‡	Cure	H	Dye test not done; patient had decidedly enlarged liver
C. L.	M, 69	Pruritus ani, psoriasis (?); many years	12	8	Vitamins and methischol ‡	?	M	Patient did not return
J. W. L.	M, 46	Hyperkeratotic dermatitis of hands; 9 yr.	32+	32	Liver extract, vitamins and methischol ‡	Treatment just begun	D	.....
S. A. L.	M, 68	Eczema; 2 mo. (face) and 3 wk. (legs)	32	24+	Liver extract, vitamins and methischol ‡	Improvement; patient still under treatment	O	Also macrocytic anemia
R. M.	M, 37	Psoriasis; 18 yr.	12	4	Liver extract, vitamins and methischol ‡	Condition improving	?	.....
S. M.	F, 57	Psoriasis; 25 yr.	12	8	Liver extract, vitamins and methischol ‡	?	D	Patient did not return
D. L. N.	M, 57	"Nummular eczema; 2 mo.	16	12	Liver extract, vitamins and methischol ‡	Cure	M	Patient had had gout 2½ years; chronic prostate infection
W. J. O.	M, 59	Eczema, hands, legs and arms; 30 yr. at intervals	24	16	Liver extract, vitamins and choline	Improvement	M	.....
R. L. P.	M, 71	Urticaria; 1 mo.	8	4	.....	.....	H	Patient did not return
O. P.	F, 53	Eczema, nondescript; 1 yr.	16	12	Liver extract, vitamins and methischol ‡	Much improvement	O	.....
G. R.	M, 70	Eczema, legs; 10 yr.	16	8	Liver extract, vitamins and methischol ‡	Pronounced improvement	H	.....
J. R.	M, 70	Seborrheic dermatitis, face and scalp; 2 mo.	40	24	Liver extract, vitamins and methischol ‡	Much improvement	O	.....

E. F. R.	M, ?	Psoriasis, scalp and anus; 2 yr.	32	20	Liver extract, vitamins and choline	No change	H	Patient discontinued treatment after third visit
J. R.	M, 60	Localized neurodermatitis of legs; 5 yr.	8	4	Liver extract, vitamins and methischol ‡	Improvement	L	.....
L. R.	F, 77	Psoriasis; 60 yr., acute 1 mo.	16	8	Liver extract vitamins and methischol ‡	Near cure	O	Acute generalized exacerbation of psoriasis
C. A. S.	F, 46	Seborrheic dermatitis; 9 mo.	8	4	Liver extract, vitamins and methischol ‡	Improvement	O	.....
D. H. S.	F, 75	Eczema, legs; 2-3 mo.	8	4	Vitamins and methischol ‡	Near cure	O	.....
H. S.	M, 41	Acne rosacea; many years	8	4	Liver extract and vitamins	Much improvement	H	.....
C. W. T.	M, 52	Eczema, legs; 5 mo.	8	4	Liver extract, vitamins and methischol ‡	Much improvement	O	.....
R. O. T.	M, 22	Seborrheic dermatitis, scalp and face; 6 mo.	8	4	Liver extract, vitamins and methischol ‡	No improvement	L	.....
H. V.	M, 32	Psoriasis; 4 yr.	24	16	Liver extract, vitamins and choline	Pronounced improvement, then relapse	H	.....
V. T.	F, 44	Psoriasis; 4 yr.	12	4	Liver extract, vitamins and methischol ‡	?	L	Patient did not return
C. V.	M, 67	Hyperkeratotic dermatitis of hands, eczema; 1 yr.	20	12	Liver extract, vitamins and methischol ‡	Improvement; patient still under treatment	D	.....
B. C. W.	M, 38	Eczema, nondescript; 7-8 wk.	8	4	Liver extract, vitamins and methischol ‡	Much improvement	H	.....
S. W.	F, 71	Eczema, face, arms and hands; 4 yr.	16 8	8 2+	Liver extract, vitamins and methischol ‡	Cure	?	Patient also sensitive to black dye; second test one year after first
B. B.	M, 40	Acne urticatus; 4-5 yr. at intervals	16	8	Improvement before liver therapy, began calcium, hapamine ‡ and roentgen ray therapy	Patient discontinued treatment	H	.....
B. B.	F, 63	Flexural dermatitis (seborrheic dermatitis); 15 yr.	32	24	Patient referred to family physician for treatment	Not known	O	.....
N. B.	M, 61	Flexural dermatitis, perianal; psoriasis (?)	16	8	Liver extract, vitamins and methischol ‡	Improvement	O	.....
J. B.	F, 43	Psoriasis; 4 yr.	8	4	Liver extract, vitamins and methischol ‡	Improvement	L	.....
F. B.	M, 57	Prurigo (?); 3 mo.	8	4	Liver extract, vitamins and methischol ‡	Not known	O	Patient discontinued treatment after second visit
A. D.	M, 22	Urticaria; 2½ yr.	8	4	None	.....	M	Patient did not return for treatment
L. E.	M, 27	Psoriasis; 3 yr.	8	4	Liver extract, vitamins, methischol ‡ and choline	No improvement	M	.....

* Treatment in all these cases included a diet high in protein and low in fat, with an abundance of fresh fruit and vegetables, and the avoidance of alcohol.
† The amount of alcohol used is indicated as follows: O, none; M, moderate; L, light; D, daily, and H, heavy.
‡ Registered trademark.

TABLE 2.—*Observations Concerning Patients Showing Defective Liver Function as Revealed by Sulfobromophthalein Test Using Five Milligrams of Dye per Kilogram of Weight Intravenously (Comparator Block Method)—Continued*

Case	Sex, Age	Diagnosis and Duration of Condition	Dye Retention, %		Treatment *	Result	Use of Alcohol †	Remarks
			30 Minutes	45 Minutes				
H. W. F.	M, 49	Eczematous and hyperkeratotic dermatitis of hands; 2 yr.	10	5	Liver extract, vitamins and methischol ‡	No improvement	D	Patient under treatment only one month
S. F.	F, 28	Psoriasis; 6 mo.	16	8	Liver extract, vitamins and methischol ‡	Much improvement	L	Eruption widely scattered
G. O. G.	M, 67	Psoriasis; 30 yr.	20	12	Liver extract, vitamins and methischol ‡	Slight improvement	L	Eruption extensive and severe
F. H.	M, 47	Peculiar herpetiform lesions and multiple ulcers; 4 yr.	12	4	Liver extract, vitamins and methischol ‡	No improvement	D	Unusual case with obscure diagnosis
D. H.	F, 52	Psoriasis; 4 mo.	8	4	Liver extract, vitamins and methischol ‡	No improvement	M	Patient discontinued treatment after third visit
F. H.	M, 63	"Nummular eczema"; 4 mo.	..	6	Liver extract, vitamins and methischol ‡	Near cure	O	Second test three months after first
			12	4				
A. H.	F, 51	Flexural dermatitis (seborrheic dermatitis?); 8 mo.	8	4	Liver extract and methischol ‡	Improvement	M	Patient discontinued treatment after three visits
H. E. J.	M, 44	Acne rosacea; 2 mo.	32	20	Liver extract, vitamins and methischol ‡	Improvement	D	Patient still under treatment
W. J.	M, 64	Infectious eczematous dermatitis, legs and thighs; 4 mo.	12	4+	Liver extract, vitamins and choline	Improvement	O	.....
C. M. J.	M, 69	Neurodermatitis, localized; 3 yr.	16+	12	Choline and vitamins	Much improvement	M	.....
B. K.	M, 53	Seborrheic dermatitis, xanthelasma	16	8	Liver extract, vitamins and methischol ‡	Seborrheic dermatitis cured; xanthelasma unchanged	M	.....
L. K.	F, 47	Flexural dermatitis (psoriasis?)	8	4	Liver extract, vitamins and methischol ‡	Near cure	O	.....
P. L.	F, 37	Flexural dermatitis (seborrheic dermatitis)	12	8	Liver extract, vitamins and methischol ‡	Pronounced improvement	O	.....
M. W.	F, 70	Eczema, face, neck and eyelids; 1 yr.	16	12	Liver extract, vitamins and methischol ‡	Pronounced improvement	O	.....
H. W.	F, 53	Flexural dermatitis	8	4	Liver extract, vitamins and methischol ‡	Near cure	O	.....
H. D. W.	M, 69	Urticaria; 6 mo.	24	12	Liver extract, vitamins and methischol ‡	?	O	Patient did not return
P. Y.	M, 61	Purpuric dermatitis of legs; 2 mo.	8	4	Liver extract, vitamins, methischol ‡ and rutin and ascorbic acid	?	M	Patient did not return
E. Y.	F, 57	Localized scattered neurodermatitis; 6 mo.	8	4	Liver extract, vitamins and methischol ‡	Improvement	M	.....
R. O. Y.	M, 66	Eczema of legs; 4 mo.	12	4	Liver extract, vitamins and methischol ‡	Improvement	O	.....
R. R.	M, 68	Hyperkeratotic dermatitis and pompholyx, palms and soles; 2 mo.	8	4	Liver extract, vitamins and methischol ‡	Slight improvement	O	Treatment changed to Benedek's vaccine
C.	M ..	"Nummular eczema"	Other tests showed liver damage		Liver extract, vitamins and choline	Near cure	H	Patient under care of internist for liver damage

* Treatment in all these cases included a diet high in protein and low in fat, with an abundance of fresh fruit and vegetables, and the avoidance of alcohol.
† The amount of alcohol used is indicated as follows: O, none; M, moderate; L, light; D, daily, and H, heavy.
‡ Registered trademark.

degree on the extent and severity of the damage and particularly on the willingness of the patient to cooperate in the matter of diet and other hygienic measures, such as avoidance of alcohol for the rest of his life.

Only one untoward reaction was observed, and this consisted in an acute urticarial eruption which developed several minutes after the dye was injected. It disappeared, however, after an injection of epinephrine.

The following case illustrates the response of a dermatosis associated with liver damage to "liver-supporting" therapy.

CASE 2.—G. R. Z., a white man aged 43, presented a scattered eczematized and intensely pruritic eruption involving the arms, legs and trunk which had been

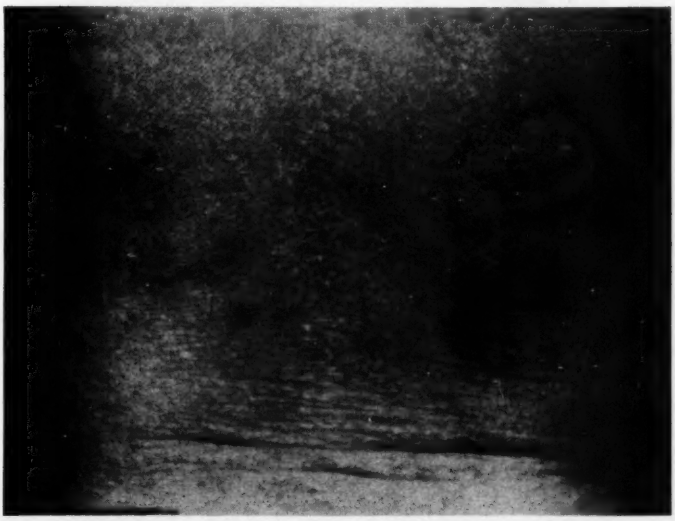

Fig. 3.—Patient J. M. B. Generalized eczematous eruption associated with decidedly defective liver function (dye retention of 40 per cent in 30 minutes and 32 per cent in 45 minutes).

present intermittently for the past six years. The eruption varied between a dry and an oozing process and had not been helped by low voltage roentgen therapy and various bland topical applications over a period of four months. The patient was a chronic alcoholic and was known to have hepatic cirrhosis. A sulfobromophthalein test revealed pronounced retention of the dye (32+ per cent at 30 minutes and 32 per cent at 45 minutes, the normal being 5 to 7 per cent at 30 minutes and 0 at 45 minutes).

"Liver-supporting" therapy was started, consisting in the administration of crude liver extract with folic acid intragluteally and methionine, inositol, choline and high potency vitamin B complex from yeast and liver with iron given orally, together with a diet low in fat and high in protein and carbohydrate and exclusion of alcohol. Within 12 days the eruption was decidedly improved, and within four

† The amount of alcohol used is indicated as follows: O, none; M, moderate; L, light; D, daily, and H, heavy.
‡ Registered trademark.

weeks it had entirely cleared. The patient remained essentially clear on this regimen for a period of about 6 months except for slight recurrences which coincided with irregularity of visits, failure to take the medication and lapses in the dietary program especially with regard to the alcohol. The patient died of unknown cause, but when he was last seen, two weeks before death, his skin was still clear except for the recent development of numerous stellate telangiectasias scattered over the back and sides of the trunk.

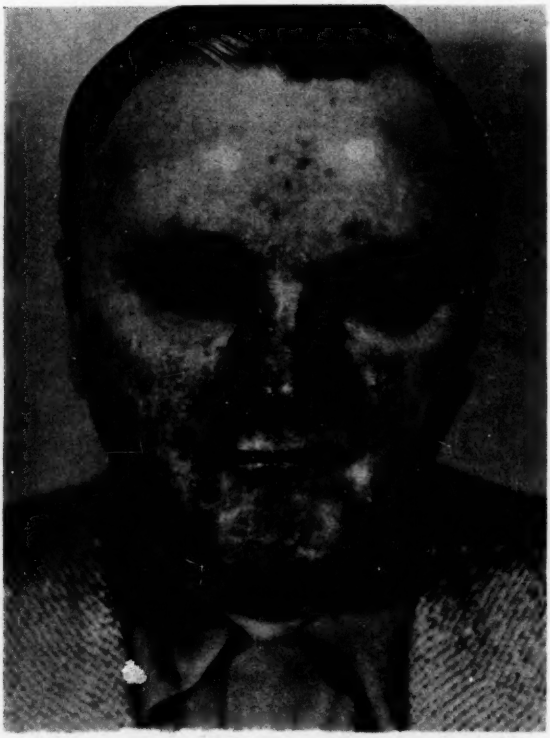

Fig. 4.—Patient H. E. J. Acne rosacea of two months' duration. Results of a sulfobromophthalein liver function test showed pronounced liver impairment, with 32 per cent dye retention at 30 minutes and 20 per cent at 45 minutes.

The above is only one of a number of cases which could be cited in support of the value of liver function determinations in certain inflammatory dermatoses of obscure etiology.

SUMMARY

Recent literature has been reviewed and two illustrative cases have been reported calling attention to the relationship between certain

inflammatory eczematous type dermatoses and nutritional disturbances involving macrocytic anemia and disturbed liver function.

Report is made of a series of 27 patients showing inflammatory dermatoses especially of an eczematous type in which macrocytic anemia was present and in which cure or improvement of the dermatoses usually followed treatment directed to the vitamin deficiency associated with the anemia.

Another series of 88 patients with various dermatoses especially of an eczematous type were found to have impaired liver function. In the majority of these cases cure or improvement of the dermatoses followed "liver-supporting" therapy.

ABSTRACT OF DISCUSSION

Dr. Fred M. Jacob, Pittsburgh: Dr. Ayres has called attention to some significant facts. The diagnostic procedures which he advocates are not difficult and in the opinion of most men are the best for the purpose for which they are used. P. N. Wahi cited a series of liver biopsies done on Hindus residing in Indian hopitals for various complaints. He found an amazing number of cases of low grade liver damage. High caste Brahmins, who were vegetarians, and low caste Hindus, who ate what they could get, both were affected by this condition. It might have been easier for both him and the patients if he had used a sulfobromophthalein test.

It is to be noted in Dr. Ayres' compilation of cases that a gratifying number of good results were obtained in cases in which one would expect improvement whereas in certain others that cannot be included in this category there were a few signs of improvement. This observation indicates that macrocytic anemia and chronic liver dysfunction are not necessarily primary causes in these vague eczematous conditions and may be contributing causes in a number of others. The etiological pictures of macrocytic anemia and chronic liver dysfunction are rather confused.

Discussions with internists bring out various opinions. Gastric, duodenal and liver functions are so closely linked that each is considered to be of great importance. Achylia is not a bar to some types of digestion and body maintenance, but it may be detrimental in utilization of vitamin B, particularly B_{12}, and also in the elaboration of the erythrocyte-maturing factor. Vitamin B_{12} is readily absorbed if administered with gastric juice or with partially digested protein containing some gastric juice. Parenteral administration of B_{12} is efficacious even in very small amounts. Vitamin B_{12} is present in unbelievably small amounts in certain foods, and only this amount is needed. It is not toxic, however, in large amounts. Battle gave 1,000 micrograms by mouth, of which dose he estimated 850 micrograms or more were lost in a poorly functioning stomach. The same amount was absorbed over a period of days when given intramuscularly. Triana found large doses toxic to albino mice but not to other animals. In the mice a type of pulmonary congestion developed.

Battle also stated that in certain types of macrocytic anemia satisfactory results are attained with the administration of liver and folic acid, at much less expense. Treatment with protein lysates is gratifying, but some men have expressed the belief that this therapeutic measure is unnecessary, stating that a high protein and low fat diet in combination with the administration of liver and high intake of the vitamin B complex will do. This may be true, but the administration of that

treatment is not always easy. We have found that anorexia, poor dentures and sometimes laziness and indifference to food preclude the possibility of an adequate intake of protein. The use of granular lysates containing liver has been satisfactory—and, we believe, necessary—in many cases.

The use of dilute hydrochloric acid is another procedure that is questioned. Teaspoonful doses of dilute hydrochloric acid may be called either homeopathic or placebo treatment, but clinically this treatment does seem to be of value. Perhaps the psychic factor is important here, though I have yet to find a patient who relishes hydrochloric acid. As to the dangers or value of alcohol, I do not agree with the author and others. Years ago, at a meeting of the Association of Pathologists and Bacteriologists, I heard the elder Dr. Mallory state without equivocation that in his opinion alcohol had nothing to do with cirrhosis of the liver.

To refute this statement I have found one article. I. F. Chickoff and associates showed liver damage on a high protein–high alcohol diet. However, anorexia and vomiting developed and the patients had to be maintained on forced feeding. We have found alcohol very useful in the management of dermatitis with protein deficiency, particularly in older patients. As a stimulant to appetite and probable aid to digestion it is excellent.

This presentation again calls attention to the presence of multiple and sometimes obscure etiological factors. Dr. Sulzberger has spoken of the chain that binds the body to disease. I prefer the term load or burden which crushes into disease. The conditions referred to by the present authors are a portion of the load that can be removed easily in many cases. It was a privilege to have had the opportunity to review and discuss this paper.

Dr. George C. Andrews, New York: This is a most interesting paper. Some of the pictures on the screen remind me of the Stryker-Halbeisen syndrome in the description of which originally—oh, probably eight years ago—was mentioned the macrocytic anemia in association with dermatitis on the sides of the neck and face. Many of Stryker and Halbeisen's cases resembled contact or seborrheic dermatitis. I think the syndrome should be mentioned in connection with this paper.

Just last month in New York at the New York State Medical Association meeting my associates and I presented a paper on the nutritional aspects of seborrheic dermatitis in which we described the use of vitamin B_{12} in about 120 cases of seborrheic dermatitis. We had fine results, showing that it was very good supplementary treatment. We were able to prevent recurrences and to clear up cases quickly with it. Vitamin B_{12} has an important action in the treatment of dermatitis.

Dr. Harry L. Arnold Jr., Honolulu, Hawaii: I was interested in the objective proof of liver damage in these cases because in similar cases I have, partly on empirical grounds, been using crude liver extract with considerable success for some years, and I should like to offer for your consideration a hypothesis of the relationship of liver damage to the occurrence of these diseases and their improvement under crude liver extract therapy.

The liver is the principal esterifying organ, as mentioned by Dr. Rothman yesterday. It has been shown by Jerome Conn and some others that esterified cholesterol is one building material from which the cortical hormones are constructed. The depression of that substance in the blood, which is to be expected in liver damage, might interfere with the production of those hormones. It is possible that the administration of crude liver extract and other supportive measures of that sort would increase the esterification of cholesterol and thus increase the

production of steroid hormones which have a very broad and general and somewhat nonspecific healing effect on quite a variety of conditions.

DR. NORMAN N. EPSTEIN, San Francisco: Dr. Ayres has added another excellent paper to a series of reports on this subject that have been presented before this Association in the past few years, including those of Andrews, Eichenlaub, Keim and Guy. Anyone who attempts to determine hepatic dysfunction by various tests runs into considerable difficulty because the liver is an organ that can function on very little normal tissue. The functions of the liver are so varied that a single test or a group of tests often fails to give accurate information concerning the status of that organ.

I have been struck with the fact that as my associates and I made rounds in the county hospital a large number of cases of liver disease were seen without evidences of dermatitis. Rosacea, spider angiomas, palmar erythema and pruritus are seen regularly, but not dermatitis. The group of cases that Dr. Ayres has discussed seem to fall into a definite class. In this type of case the patient rarely has a severe liver disease.

That observation does not mean, however, that here are no changes in function. The macrocytic anemia, edema and hepatic dysfunction are the results rather than the cause. The main basis for the disturbance is the nutritional disturbance. The correction of those factors usually gives satisfactory therapeutic results.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: The liver can withstand a great amount of damage, and its ability to regenerate is remarkable, as has been demonstrated by Mann and co-workers. In cases of borderline hepatic dysfunction we are not justified in placing too much emphasis on conventional tests for measuring liver function. There is one test that can be used, which has been emphasized by Watson and others, and that is the measure of the excretion of coproporphyrin in the urine and the analysis of the isomers, such as has been done in the study of cirrhosis, infectious hepatitis and even certain infectious diseases such as acute anterior poliomyelitis. In general, the use of liver extract and folic acid has been extended without discrimination to the treatment of patients with miscellaneous disorders, largely on an empirical basis, and in my opinion has been greatly overdone. We should go slow in drawing conclusions on the effects of these substances in benefiting clinical disorders in which the evidence of hepatic damage is questionable.

DR. SAMUEL AYRES JR., Los Angeles: I appreciate the remarks of the discussants, and I also should like to emphasize that I do not feel that we have any kind of a panacea here. I certainly would be the last one to attribute too much significance to tests showing borderline results. I think perhaps a more extensive battery of liver function tests should be employed.

However, in the literature it has been stated on several occasions that while some of the tests, like the cephalin flocculation and thymol turbidity tests, are of comparable value in early liver damage, the sulfobromophthalein test is the most valuable one in detecting chronic liver damage with cirrhosis. In reference to Dr. Andrews' remarks concerning the similarity of the lesions in some of the patients with macrocytic anemia to those cases reported by Stryker and Halbeisen, I referred to that in the paper and went into a little more detail concerning the types of lesions which these authors described. I think that the eruption in some of our cases did correspond in many ways to that described by Stryker and Halbeisen.

I have not seen in dermatological literature, however, any confirmatory work along these lines, and I believe this point is an important aspect of eczematous and perhaps other types of dermatoses which has been overlooked.

Ordinary routine blood counts as done by the average laboratory completely ignore the mean corpuscular volume, and yet its determination is an extremely simple thing to do. If we will get into the habit of performing determinations for mean corpuscular volume and mean corpuscular hemoglobin concentration as a routine in a blood examination we will observe more of these cases of macrocytic anemia. Incidentally, the actual anemia in many of these patients may be relatively mild, and yet there may be a definite macrocytic picture, and the nutritional factors as evidenced in the hemogram will show striking improvement with treatment.

Another aspect in the defective liver function is the fact that when the liver is not functioning adequately surplus estrogens which are circulating are not destroyed and this excess of estrogens in the male may result in feminizing symptoms. This point is an interesting sidelight.

HIDRADENOMA OF THE VULVA

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LOS ANGELES

THE PURPOSE of this paper is to call the attention of dermatologists to a relatively uncommon lesion which usually involves the vulva. Very rarely, however, similar lesions are found in the axilla, on the breast and about the anus. There is only one reference in dermatologic literature to such a condition,[1] although Lever mentioned the condition incidentally in several articles which will be referred to later. However, there are numerous publications about this lesion in gynecologic and pathologic literature. The lesion referred to is termed a hidradenoma, adenoma hidradenoides or hidradenoma tubulare. It is an important condition because, although benign, it is often mistaken in both its clinical and histopathologic aspects for an adenocarcinoma.

HISTORICAL REVIEW

Werth[2] is generally credited with the first description of hidradenoma of the vulva. It is difficult from his work to verify this priority. However, there is no doubt that the condition was recognized by Braun[3] and Gebhard[4] before the turn of the century.

Single cases were reported early by Schickele[5] and MacGregor.[6] It remained, however, for Pick[7] in 1904 to separate these lesions into a

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 20, 1950.

1. Woringer, F.: Sweat Gland Adenoma in a Small Tumor of the Labia Majora, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **45**:112 (Feb.) 1938.

2. Werth, R.: Anatomy of Cysts of the Vulva, Zentralbl. f. Gynäk. **2**:513, (Oct. 26) 1878.

3. Braun, H.: Endothelioma of the Skin, Arch. f. klin. Chir. **43**:196, 1892.

4. Gebhard, C.: Pathologic Anatomy of the Female Sex Organ, Leipzig, S. Hirzel, 1899, vol. 16, p. 591.

5. Schickele, G.: Further Contribution to the Knowledge of Mesonephric Tumors, Beitr. z. Geburtsh. u. Gynäk., Leipzig **6**:449, 1902.

6. MacGregor, J. M.: Papillary Cyst of the Labium Minus, Scottish Med. & Surg. J. **13**:140 (Aug.) 1903.

7. Pick, L.: A Special Form of Nodular Adenoma of the Vulva, Arch. f. Gynäk. **71**:347, 1904; Hidradenoma and Adenoma Hidradenoides, Virchows Arch. f. path. Anat. **125**:312, 1904.

distinct category. In two articles and on the basis of two cases as well as those previously reported he designated the condition as (1) hidradenoma, which he believed to arise from fully formed sweat glands, and (2) adenoma hidradenoides, which he believed to arise from the epidermis or at least from incompletely formed sweat glands. It is important to note that he did remark on the double layer of cells lining the acini and furnished six drawings detailing the characteristic histology. In fact, one of his figures was used in Jadassohn's "Handbook"[8] to portray this condition.

After Pick's distinct contribution, cases were reported in the foreign literature in increasing numbers by Fleischmann,[9] Williamson,[10] Gross,[11] Bondi,[12] Schröder,[13] Stern [14] and Frattin.[15] It was not until 1915 that a typical case was reported from this country, by Outerbridge,[16] who reviewed the literature up to that time.

Additional reports involving one or more typical cases were by Köhler,[17] Kehrer,[18] Schwarz,[19] Meyer,[20] Wrigley,[21] Arns,[22] Hoeck,[23] Kowalewicz,[24] Blau [25] and Dougal.[26]

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8. Beck, S. C.: Epithelioma, in Jadassohn, J.: Handbook of Skin and Venereal Diseases, Berlin, Springer-Verlag, 1933, vol. 12, pt. 3, p. 461.

9. Fleischmann, C.: Contribution to the Case Histories of Adenoma Hidradenoides Vulvae, Monatsschr. f. Geburtsh. u. Gynäk. **21**:497, 1905.

10. Williamson, H.: A Note on Adenoma of the Vulva, J. Obst. & Gynaec. Brit. Emp. **10**:253 (Sept.) 1906.

11. Gross, E.: Multiple Benign Tumors of the Vulva (Adenoma Hidradenoides), Ztschr. f. Geburtsh. u. Gynäk. **60**:565, 1907.

12. Bondi, J.: The Anatomy of Cysts of the Small Labia, Monatsschr. f. Geburtsh. u. Gynäk. **28**:648, 1908.

13. Schröder, R.: Cystadenoma Hidradenoides of the Vulva, Zentralbl. f. allg. Path. u. path. Anat. **22**:529, 1911.

14. Stern, R.: Adenoma Hidradenoides Vulvae, Monatsschr. f. Geburtsh. u. Gynäk. **39**:707, 1914.

15. Frattin, G.: Contribution to the Knowledge of Sweat Gland Adenoma, Arch. f. klin. Chir. **106**:522, 1915.

16. Outerbridge, G. W.: Sweat-Gland Tumors of the Vulva (Adenoma Hidradenoides Vulvae), Am. J. Obst. **72**:32 (July) 1915.

17. Köhler, R.: Sweat Gland Adenoma of the Vulva, Monatsschr. f. Geburtsh. u. Gynäk. **44**:493, 1916.

18. Kehrer, E.: Sweat Gland Adenoma of the Vulva, Zentralbl. f. Gynäk. **43**:339, 1919.

19. Schwarz, E.: Case of Adenoma Hidradenoides Tubulare Destruens, Am. J. Obst. & Gynec. **1**:695, 1921.

20. Meyer, R.: Sweat Gland Proliferation and Hidradenoma of the Vulva: 4 Cases, Ztschr. f. Geburtsh. u. Gynäk. **86**:420, 1922.

21. Wrigley, A. J.: Two Cases of Adenoma of the Vulva, Proc. Roy. Soc. Med. **22**:1439 (Sept.) 1922.

22. Arns, G.: Papillocystoma in the Labium Majus, Monatsschr. f. Geburtsh. u. Gynäk. **67**:1, 1924.

23. Hoeck, W.: A Case of Tubular Hidradenoma of the Vulva, Zentralbl. f. Gynäk. **50**:2757 (Oct. 23) 1926.

Since 1930 there have been additional reports, by Midana,[27] Taddei,[28] Eichenberg,[29] Rothman and Gray,[30] Folsome,[31] McDonald,[32] McDonald, Lovelady and Waugh,[33] Gilbert,[34] Danforth,[35] Gardner,[36] Lash,[37] Novak and Stevenson,[38] Lacy,[39] Prakken,[40] De Giorgi,[41] Brattström,[42] Boscence [43] and Cunningham and Hardy.[44]

All told, there are about 100 such cases reported in the world's literature. There is such remarkable agreement as to the clinical appear-

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24. Kowalewicz: Three Cases of Adenoma Hidradenoides Vulvae, Inaug. Diss. Breslau, 1926; cited by Hoeck.[23]

25. Blau, A.: Hidradenoma Vulvae, Ztschr. f. Geburtsh. u. Gynäk. **93**:341, 1928.

26. Dougal, D.: Hydradenoma of the Vulva, J. Obst. & Gynaec. Brit. Emp. **37**:406, 1930.

27. Midana, A.: Tubular Hydradenoid Adenoma of the Vulva, Cancro, Tor. **2**:156, 1931; abstracted, Am. J. Cancer **16**:431, 1932.

28. Taddei, A.: Adenoma of the Sudoriparous Glands of the Labium, Clin. ostet. **36**:220, 1934; abstracted, Am. J. Cancer **26**:461, 1936.

29. Eichenberg, H. E.: Hidradenoma Vulvae, Ztschr. f. Geburtsh. u. Gynäk. **109**:358, 1934.

30. Rothman, D., and Gray, S. H.: Hidradenoma of the Vulva, Am. J. Obst. & Gynec. **38**:509 (Sept.) 1939.

31. Folsome, C. E.: Benign and Malignant Tumors of the Vulva, J. A. M. A. **114**:1499 (April 20) 1940.

32. McDonald, J. R.: Apocrine Sweat Gland Carcinoma of the Vulva, Am. J. Clin. Path. **11**:890, 1941.

33. McDonald, J. R.; Lovelady, S. B., and Waugh, J. M.: Adenocarcinoma of the Vulva, Am. J. Obst. & Gynec. **42**:304 (Aug.) 1941.

34. Gilbert, B.: Contributions to Gynecological Pathology, J. Obst. & Gynaec. Brit. Emp. **48**:511, 1943.

35. Danforth, W. C.: Hydradenoma Vulvae, Am. J. Obst. & Gynec. **43**:329 (Feb.) 1943.

36. Gardner, G. H., in discussion on Danforth.[35]

37. Lash, A. F., in discussion on Danforth.[35]

38. Novak, E., and Stevenson, R. R.: Sweat Gland Tumors of the Vulva: Benign (Hidradenoma) and Malignant (Adenocarcinoma), Am. J. Obst. & Gynec. **50**:641 (Dec.) 1945.

39. Lacy, G. R., Jr.: Hydradenoma and Hydradenoid Carcinoma of the Vulva, Am. J. Obst. & Gynec. **51**:268 (Feb.) 1946.

40. Prakken, J. R.: Syringo-Steato-Adenoma Papilliferum Cysticum Vulvae, Acta dermat.-venereol. **27**:432, 1947.

41. De Giorgi, L.: Sudoriferous Gland Tumors on the Labia, Arch. ostet. e ginec. **51**:119 (March-April) 1946; abstracted, Am. J. Obst. & Gynec. **55**:905 (May) 1948.

42. Brattström, H.: Tumors of Sweat Glands in Vulva, Nord. med. **41**:987 (June 3) 1949; abstracted, J. A. M. A. **141**:878 (Nov. 19) 1949.

43. Boscence, B.: A Case of Hidradenoma of the Vulval Region, M. J. Australia **2**:850 (Dec. 10) 1949.

44. Cunningham, J. A., and Hardy, J.: Hidradenomas of the Vulva: Report of 4 Cases with an Evaluation of Them in the Light of Analogous Breast Lesions, South. Surgeon **13**:831 (Nov.) 1947.

ance and microscopic observations in this condition that there is little doubt that it constitutes a disease entity. There is, however, disagreement as to the origin of these lesions, their malignant potentialities and their relationship to other somewhat similar and probably closely related conditions.

CLINICAL FEATURES

From a clinical standpoint hidradenoma of the vulva is most frequently located on one of the labia majora. It is much less common on one of the labia minora and is relatively rarely found in the sulcus between the greater and lesser lips.

In the vast majority of cases the lesion is solitary, although multiple lesions have been reported.[45] It is usually asymptomatic, but both pain and slight bleeding may occur.

The lesion is a sharply circumscribed round or ovoid tumor mass or nodule measuring from 0.5 to 1.5 cm. in diameter. It may simulate a fibroma or a sebaceous cyst, being slightly elevated above the surrounding surface. Sometimes the overlying skin and the tissue has extruded through the opening to form a red, granular, small raspberry-like lesion with a broad pedicle, which simulates a pyogenic granuloma.

In many cases hidradenoma of the vulva has been found accidentally during operations involving plastic repair of the pelvic outlet. The significance of the fact that this lesion has not been described in the Negro race is unknown, although both Novak and Stevenson [38] and Cunningham and Hardy [44] had access to such material. No cases have been reported prior to puberty, most examples of the condition having occurred in the 40 to 50 year age group.

Since 1938, when I saw my first example of this rare lesion, I have been able to collect histopathologic material from three additional cases as well as from two similar lesions involving the nipple.

HISTOLOGY

As an aid in understanding such a lesion it seems worth while to give a brief review of the different types of cutaneous glands.

Maximow [46] divided the cutaneous or exocrine glands into three groups, as follows: (1) the merocrine glands, or those in which the epithelium remains intact during secretion, eccrine and epicrine being other names applied to this group, to which ordinary sweat glands belong; (2) the apocrine glands, or those in which portions of the cell cytoplasm are extruded to form the secretion, and (3) the holocrine glands, or those in which the epithelial cells degenerate completely during

45. Pick.[7] Gross.[11] Cunningham and Hardy.[44]

46. Maximow, A. A., and Bloom, W.: Textbook of Histology, ed. 5, Philadelphia, W. B. Saunders Company, 1948, p. 288.

Differences Between Apocrine and Eccrine Sweat Glands

Apocrine Glands	Epicrine - Eccrine - Merocrine
Embryology	
From primary germ of the epithelium, e. g., from already differentiated epithelium	From undifferentiated epithelium
Development	
Small and underdeveloped before puberty; enlarge and become actively secreting only when puberty reached; not reduced in number or size in old age	Well developed at birth
Anatomy	
Abrupt enlargement where duct joins secretory part of gland	No enlargement where duct joins secretory part of gland
Type	
Large compound tubular type	Ordinary simple tubular type
Location	
Axilla, breast, pubovulvar and perianal; apocrine glands undoubtedly occur in uncommon areas	Entire cutaneous surface except nails, labia minora, inner surface of prepuce, glans and internal part of pinna of ear
Color	
Reddish tint	Yellowish
Size	
50 mm. long, 2 mm. wide, 3 to 5 mm. thick; individual glands larger than those of simple sweat glands	0.1 to 0.5 mm. to 1 to 4 mm. or more
Depth	
Extend deeply and reach as far as subcutis	Entirely in cutis
Association with hair	
Close association with hair sheaths; duct may open into cavity of sheath; more frequently opens in a depression in the epidermis close to point where hair issues	No association with hair sheaths; opens directly onto surface of skin
Finer anatomy	
Gland cells bound by basement membrane; myoepithelium present between the gland cells and the basement membrane; lining or glandular cells one layer thick and of two types—(*a*) in resting stage are cuboidal with clear cytoplasm and (*b*) if actively secreting are columnar and cytoplasm full of granules, with nucleus central in resting stage, toward base in secreting stage; act of secretion accompanied with an accumulation of granules near surface of cell which projects far out into the lumen; secretion actually liberated into the lumen by the rupture and fragmentation of the projecting part of the cell—e. g., the cell actually loses a volume of its protoplasm.	Gland cells bound by membrane; myoepithelium present between basement membrane and single layer of glandular cells; secretion is a fluid formed as little droplets within the cell protoplasm; pushed out into the lumen of the gland without any loss of protoplasmic substance—e. g., secretion is more fluid—eccrine glands at times may be capable of forming and giving forth a cellular secretion similar to that of apocrine glands
Staining with hematoxylin and eosin	
Glands take the eosin	Glands stain deeply with the hematoxylin
Granules	No iron present in secreting cells
(*a*) Intracellular yellowish pigment; (*b*) stain light brown with osmic acid; (*c*) positive for iron with Turnbull's blue, Mallory's ammonium sulfide and ferrocyanide	

secretion and are discharged as the secretion, the sebaceous glands belonging to this group.

The differences between eccrine and apocrine sweat glands are well summarized in the accompanying table, which was assembled from the excellent contributions of Woolard,[47] Way and Memmesheimer [48] and Henke and Lubarsch.[49] (Transitional forms between the two types probably occur.)

The histopathological observations in hidradenoma of the vulva are quite characteristic, although considerable variations occur. At the onset the lesion is usually located in the cutis with an intact overlying epi-

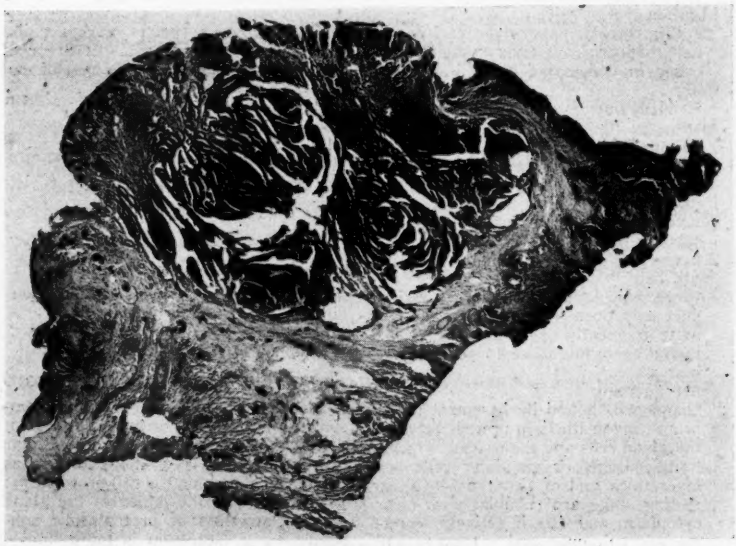

Fig. 1.—Low power view of hidradenoma of the vulva, showing characteristic circumscribed papillary growth which has eroded the overlying epidermis and partially extruded through the resultant opening.

dermis. Innumerable irregular acini and tubules which are separated by delicate connective tissue septums make up the general structure. In the commonest type one finds these intricate and irregular papillary and

47. Woolard, H. H.: The Cutaneous Glands of Man, J. Anat. **64**:415, 1930.

48. Way, S. C., and Memmesheimer, A.: The Sudoriparous Glands: The Eccrine Glands, Arch. Dermat. & Syph. **34**:797 (Nov.) 1936; The Sudoriparous Glands: The Apocrine Glands, ibid. **38**:373 (Sept.) 1938.

49. The Apocrine Sweat Glands, in Henke, F., and Lubarsch, O.: Handbook of Special Pathologic Anatomy and Histology, Berlin, Springer-Verlag, 1933, vol. 7, pt. 2, p. 36.

adenomatous structures either definitely enclosed within a cyst wall or in the form of a fairly well circumscribed lesion surrounded by a fibrous capsule.

Since the contribution of Pick [7] it has been noted that frequently but not always there are two layers of epithelial cells covering the papillary projections and lining the acini. There is an inner layer of tall columnar or cylindrical cells which line the lumen of the acini. These take an acidophilic stain. These cells have a vesicular nucleus located either near the middle or toward the base of the cell. The second layer, or outer

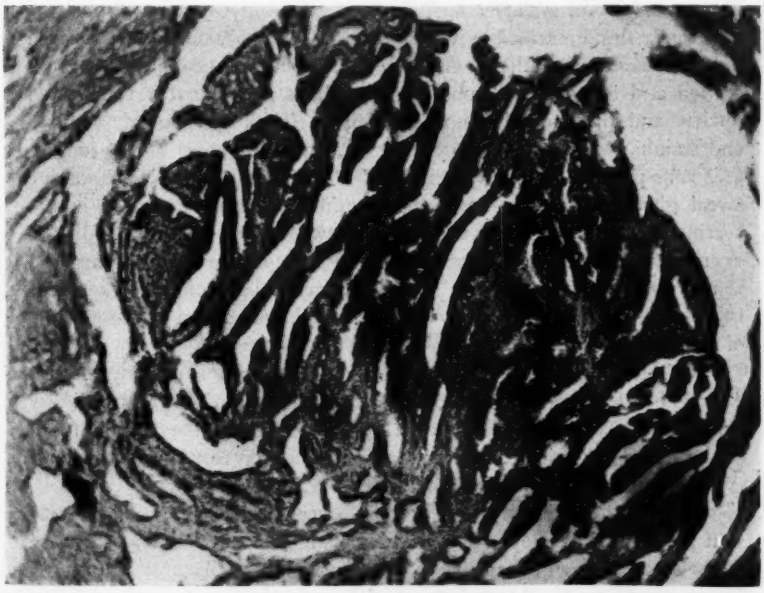

Fig. 2.—High power view of a portion of figure 1, showing the predominant papillary structure with few adenomatous elements.

row of cells, is smaller, with more irregularly shaped cells, and presents closely packed, small, dark nuclei surrounded by a small amount of protoplasm. This is the myoepithelial layer, which rests on the basement membrane. This layer may be lacking in some of the acini, especially in the larger ones. For the most part the acini and cysts are empty, but here and there they do present fine granular contents and desquamated epithelium.

There is one histological type which is quite rare and in which the structure is that of a tubular adenoma. Cases of this type have been presented by Hoeck,[23] Danforth,[35] Stern [14] and Taddei.[28]

In general, however, the histological picture with both low and high power magnification is so characteristic that photomicrographs or drawings from all the reported cases could be used interchangeably.

HISTOGENESIS (PATHOGENESIS)

There is more or less general agreement in the idea first advanced by Pick that these tumors originate from sweat glands. He repeatedly stressed the double layer of cells present in some sweat glands as well as in the acini of these tumors. He noted that there was a layer of "ectodermal muscle cells" seen between the epithelium and the membrana propria of certain sweat glands. This so-called myoepithelial layer was apparently first described by von Koelliker [50] in 1852. Sheldon [51] pointed out that these myoepithelial cells are spindle shaped, triangular on cross section and 30 to 90 microns long and have an elongated rod-shaped nucleus and longitudinal cytoplasmic fibrils. Their morphologic features and staining qualities are those of smooth muscle fibers. Their longest axis runs parallel or slightly tangential to that of the gland. In apocrine sweat glands they form an almost continuous outer layer, but in the eccrine sweat glands there are spaces between the single cells. In the excretory ducts of the eccrine glands the myoepithelium disappears and is replaced by a second layer of epithelial cells. The function of these myoepithelial cells is to aid, by contraction, the expulsion of the product of the gland.

While the double layer of cells present in the acini of many hidradenomas of the vulva does not exclude their possible origin from ordinary or eccrine sweat glands, it would seem to exclude the possibility of sebaceous gland origin. The latter view was expressed by Kreibich,[52] Arzt and Kumer,[53] Wrigley [21] and Teacher.[54]

Prakken [40] expressed the same opinion as Fischer, that many nevoid skin conditions develop from the epithelial primordium. He included epithelioma adenoides cysticum of Brooke, hidradenoma eruptif of Jacquet-Darier, nevus follicularis and nevus sebaceus in this group of disorders. This primary germ of the epithelium is a downgrowth of epidermis which appears between the second and fourth months of embryonic life. From this primordium an outgrowth which may develop into an apocrine sweat gland and another which is the beginning of a

50. von Koelliker, R. A.: Handbook of Human Histology, translated by G. Busk and T. Huxley, London, Sydenham Society, vol. 1, 1853, p. 203.

51. Sheldon, W. H.: The Myoepithelium In Sweat Gland Tumors: Distribution, Histology, Embryology and Function, Arch. Path. **31**:326 (March) 1941.

52. Kreibich, cited by Beck.[8]

53. Arzt and Kumer, cited by Beck.[8]

54. Teacher, J. H.: A Manual of Obstetrical and Gynaecological Pathology, London, Oxford University Press, 1935, p. 385.

sebaceous gland form; the latter structure also forms the hair. Thus the primordium can develop not only into a follicle with a sebaceous and an apocrine sweat gland but also into a free sebaceous gland such as is found in the areola of the nipple.

On the basis that definite sebaceous gland cells were present in his case along with sweat gland elements, as well as evidence of holocrine secretion, Prakken expressed the opinion that at least in his case the lesion originated from the primordium of the hair follicle, sebaceous gland and apocrine sweat gland with disturbance of development in this primordium at an early age. The simultaneous occurrence of a nevus syringocystadenomatosus papilliferus and a sebaceous nevus as reported by Marcus and Wooldridge [55] would support such an idea.

Such a theory, however, does not seem to explain the clinical facts that these lesions appear only in adult life and that for all practical purposes they are found mostly about the vulva. One such lesion has been reported about the anus,[56] and I have seen two instances of such lesions involving the nipple. Nor does such a theory explain the occurrence of nevus syringocystadenomatosus papilliferus on the sole, a site on which I have seen such a condition. Surely this is an area where hairs, sebaceous glands and apocrine glands are not supposed to occur.

In general it may be stated that most pathologists, including gynecologic pathologists, have expressed the belief that hidradenomas of the vulva develop from apocrine sweat glands. This idea was first advanced by McDonald.[32] Lever [57] in several communications also has expressed such a belief. However, one must agree with Novak and Stevenson that it is probably not correct to assume that such hidradenomas are always of apocrine gland origin. Since I first became aware of this entity in 1938, I have been on the alert in an attempt to find similar lesions involving the axilla. This attempt has been mostly without success from a clinical standpoint. In a fairly complete review of the literature I have been able to find only one probable case involving the axilla. This, reported by Robinson,[58] was of a lesion the size of a Barcelona nut located in the skin of the outer wall of the left axilla in a girl 13 years

55. Marcus, M. D., and Wooldridge, W. E.: Sebaceous Nevus and Nevus Syringocystadenomatosus Papilliferus Occurring as a Mixed Form: Report of a Case, Arch. Dermat. & Syph. **61**:105 (Jan.) 1950.

56. Cooper, W. L., and McDonald, J. R.: Adenoma of the Apocrine Sweat Glands (Hidradenoma) of the Anal Canal, Arch. Path. **38**:155 (Sept.) 1944.

57. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949, p. 303; Pathogenesis of Benign Tumors of Cutaneous Appendages and of Basal Cell Epithelioma, Arch. Dermat. & Syph. **57**:679 (April) 1948; Myoepithelial Sweat Gland Tumor: Myoepithelioma; Report of 3 Cases with a Review of the Literature, ibid. **57**:332 (March) 1948.

58. Robinson, H. B.: Papilliferus Cyst of a Sudoriparous Gland from the Axilla, Tr. Path. Soc. London **49**:290, 1898.

of age. The pathologic picture was described as that of a papilliferus cyst of a sudoriparous gland. Histologically there were cystic spaces lined by epithelial cells which were two to three layers thick. No drawings of the microscopic observations were presented.

No present theory of the pathogenesis explains the absence of hidradenoma of the vulva in the Negro, whose apocrine glands are three times more numerous than the white person's. Nor do any theories explain why no similar corresponding lesion has been seen in the male. Certainly Fox-Fordyce disease is a disorder of the apocrine glands, and, while it usually occurs in the female, instances have been reported in the male, especially among the Japanese.[59]

QUESTION OF MALIGNANCY OF HIDRADENOMA VULVAE

In only one work, that of McDonald and co-workers,[32] were these lesions considered malignant. The authors expressed the belief that all such lesions as have been described were adenocarcinomas of the vulva. Of 30 cases presented from the Mayo Clinic, 28 were classified as grade 1 (Broders) and two as grade 2.

In spite of the fact that Broders was said to be in agreement with this concept,[60] no one else has accepted it. In fact, Gates, Warren and Warvi,[61] in citing McDonald's work, specifically stated that "the majority of tumors described as adenocarcinoma of the vulva are benign and should be considered hydradenoma papilliferum." Gray [62] accepted only the two obvious cases of malignant growth from among the 30 lesions reported by McDonald. He pointed out that the lesions were slow growing, they had existed for many years, metastases did not occur, mitotic figures were rare, the lesions were cured by simple excision and recurrences were not found.

Novak and Stevenson [38] criticized Folsome [31] for saying that 27 per cent of the tumors were locally invasive and therefore presumably malignant. They also expressed the opinion that a disservice had been rendered by McDonald [32] and McDonald, Lovelady and Waugh [33] in flat-footedly designating these tumors adenocarcinomas. He accepted their two undoubtedly malignant cases but pointed out that these two were of unknown histogenesis. Novak further reviewed carefully the original reports in the literature of the four cases considered malignant. He

59. Dohi, S.: Fox-Fordyce Disease, Arch. f. Dermat. u. Syph. **159**:611, 1930.

60. McDonald, J. R.: Adenocarcinoma of the Vulva, Correspondence, Am. J. Obst. & Gynec. **43**:179 (Jan.) 1942.

61. Gates, O.; Warren, S., and Warvi, W. N.: Tumors of Sweat Glands, Am. J. Path. **19**:591 (July) 1943.

62. Gray, S. H.: Adenocarcinoma of Vulva, Correspondence, Am. J. Obst. & Gynec. **43**:178 (Jan.) 1942.

concluded that the cases of Ruge,[63] Schiffman[64] and Burg[65] were not malignant. In Eichenberg's[29] case malignancy was present beyond a doubt, but no histologic appearances were given.

Novak went on to say that in "only one case in the world's literature has malignancy appeared to develop in a hidradenoma. Even this assumption may not be correct as the tumor may have been definitely malignant from the onset. In other words adenocarcinoma may arise directly from sweat glands just as the benign hidradenoma does and not necessarily with the intermediation of the latter." In fact, primary adenocarcinoma of the vulva is exceedingly rare.

Lacy's[39] second case was possibly a Bowenoid type of epithelioma and not a hidradenoid carcinoma, as reported. It is also difficult to accept the first case of Cunningham and Hardy[44] as having developed from a true hidradenoma of the vulva.

Sheldon's[51] case 2, which he stated the opinion presented a tumor of low grade malignancy and which he called a papillary hidradenocarcinoma, was most likely a hidradenoma of the vulva.

RELATIONSHIP TO NEVUS SYRINGOCYSTADENOMATOSUS PAPILLIFERUS

When one considers hidradenoma (vulvae) in relation to nevus syringocystadenomatosus papilliferus one can, among other viewpoints, take that of Gates, Warren and Warvi,[61] who expressed the opinion that the two conditions are identical and of either eccrine or apocrine sweat-gland origin. These authors apparently gave either lesion the designation hydradenoma papilliferum. In fact they stated that their superficial type of hydradenoma papilliferum "has been commonly known as naevus syringocystadenomatosus papilliferus." They further qualified this idea, however, by stating that the only relationship is a similarity of the type of growth. As to the differences, they pointed out that the superficial types of hydradenoma papilliferum are often associated with inflammation, that the superficial and intermediate types have characteristics suggesting a congenital malformation, that the deep tumors are more complex neoplasms, probably acquired, and, finally, that there are atypical forms which do not fit in any group.

There are other authors, however, who would distinctly separate hidradenomas (of the vulva) from nevus syringocystadenomatosus

63. Ruge, H.: Vulvar Affections and Their Gynecologic Importance (Sweat Gland Carcinoma), Ztschr. f. Geburtsh. u. Gynäk. **56**:307, 1905.

64. Schiffman, J.: Sweat Gland-Tissue Cancroid in the Vulva, Zentralbl. f. Gynäk. **44**:59 (Jan. 17) 1920.

65. Burg, E.: A Case of Adenoma Hydradenoides Vulvae, Zentralbl. f. Gynäk. **54**:395, 1930.

papilliferus. Their reasons for this distinction include the definite history that most lesions of nevus syringocystadenomatosus papilliferus have been present since birth, that clinically the appearance is often that of a nevus or birthmark, that histologically there is often a dense infiltrate of plasma cells and, finally, that a great many, if not most, of such lesions occur in regions where apocrine glands are not supposed to occur. Beck,[8] in Jadassohn's "Handbook," differentiated hidradenomas from syringadenoma papilliferum. He cited Ricker and Schwalb as also separating hidradenomas of the vulva from other sweat gland tumors because of

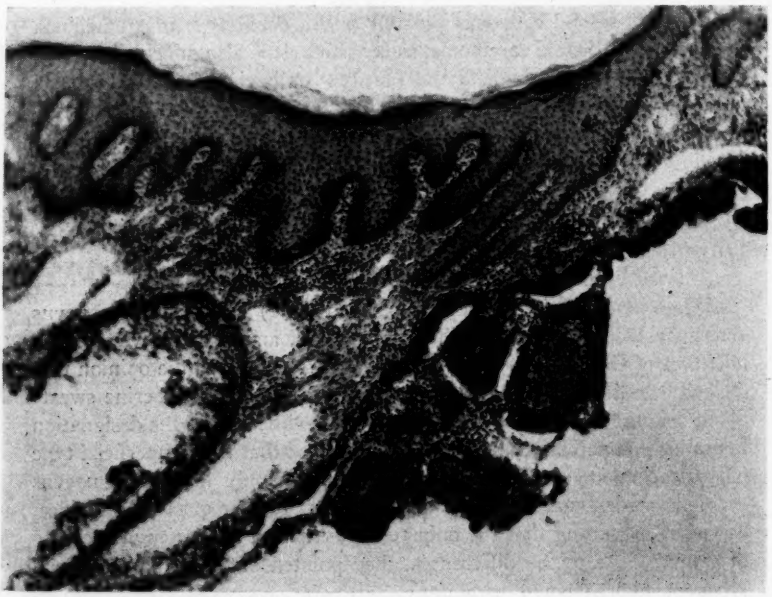

Fig. 3.—Nevus syringocystadenomatosus papilliferus, showing typical double layer of cells.

their special localization. Lever [57] stated the belief that hidradenoma papilliferum represents an adenoma of apocrine glands while nevus syringocystadenomatosus papilliferus is predominately an adenoma of apocrine ducts. Many authorities, however, expressed the opinion that nevus syringocystadenomatosus papilliferus arises from ordinary or eccrine sweat ducts. These include Gans,[66] Sachs and Lewis,[67] Car-

66. Gans, O.: Histology of Diseases of the Skin, Berlin, Springer-Verlag, 1928, vol. 2, p. 282.

67. Sachs, W., and Lewis, G. M.: Naevus Syringadenomatosus Papilliferus (Werther), Arch. Dermat. & Syph. **36**:1202 (Dec.) 1937.

denal [68] and Gates, Warren and Warvi.[61] The last-mentioned authors stated that they had

> noted single apocrine-like structures among coil glands, associated with chronic inflammation, on parts of the body where apocrine glands do not usually occur. It is a question whether this represents changed epithelium of sweat glands under abnormal conditions and, if so, whether it is properly considered a metaplastic change.

Metaplasia in sweat gland tumors was also reported by Walther and Montgomery.[69]

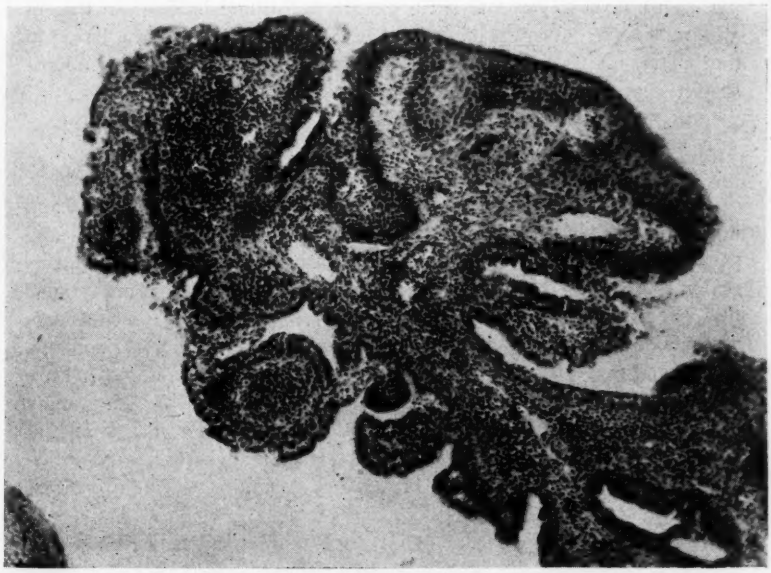

Fig. 4.—Nevus syringocystadenomatosus papilliferus, showing typical double layer of cells.

Malignant changes have been reported as occurring in nevus syringocystadenomatosus papilliferus. In Reuterwall's [70] excellent presentation large nests of basal cells at the border of the lesion in case 2 were demonstrated in a photomicrograph. In case 4 an ulcerating walled-off basal cell epithelioma was present and three months later a cancer of sebaceous

68. Cardenal, C.: Histology of Syringocystadenoma Papilliferum, Arch. f. Dermat. u. Syph. **166**:315, 1932.

69. Walther, M., and Montgomery, H.: Sweat Gland Tumor with Epithelial Metaplasia, Arch. f. Dermat. u. Syph. **163**:420, 1931.

70. Reuterwall, O.: Naevus Syringo-Cystadenomatosus Papilliferus and Its Relation to Malignancy, Acta path. et microbiol. Scandinav. 1933, supp. 16, p. 376.

gland cells was found in the same lesion but distant to the basal cell growth.

Nevertheless, there are instances in which from a histological standpoint it is difficult or even impossible to differentiate these two conditions. Such a case was presented by Darier and Hallé [71] under the designation of a benign cutaneous branchioma because of the erroneous idea that the lesion was of branchial cleft origin. Their clinical picture, reproduced by a woodcut and microscopic drawing in their figure 3, and the clinical history leave little doubt that their patient presented the entity of nevus syringocystadenomatosus papilliferus. Their second microscopic drawing, figure 4, however, showed a picture indistinguishable from that of a hidradenoma. Incidentally, case 4 of Sachs and Lewis had a lesion in the labium majus that from their description, both clinical and microscopic, cannot be differentiated from hidradenoma of the vulva.

RELATIONSHIP TO INTRADUCTAL PAPILLOMA OF THE BREAST (NIPPLE)

Apocrine sweat glands are found in the axilla, about the breast and nipple, in the abdominal wall and in the vulval, inguinal, perineal and perianal regions. Since apocrine glands are modified in the mammary region to form the parenchymatous portion of the breast, it is not strange that aside from the similar embryologic origin there should be considerable analogy between hidradenoma of the vulva and intraductal papilloma of the breast. In their clinical behavior both of these conditions (*a*) are relatively benign and slow growing, (*b*) on very rare occasions may undergo malignant change (*c*) usually are present for a long period before producing symptoms, (*d*) may produce a slight discharge which may or may not be bloody and, finally, (*e*) generally are cured on local excision.

From a histological standpoint their similarity is striking and ordinarily one cannot distinguish between the two conditions. As pointed out by Cunningham and Hardy,[44] each one is a papillary tumor growing into a lumen, the lining epithelium is double layered and in 25 per cent of cases both tumors show glands lined by light acidophilic cells with small nuclei, this feature of each tumor strikingly resembling apocrine sweat glands. Finally, cylindromatous types of sweat gland tumors occur in both vulva and breast.

Though Karsner [72] stated that intraductal papillomas should be treated as if they were potentially malignant, there are many who disagree. A

71. Darier, J., and Hallé, J.: Benign Cutaneous Branchioma (Vegetating Fistulas of the Neck and the External Ear), Ann. de dermat. et syph. series 6, **1**:1, 1920.

72. Karsner, H. T.: Human Pathology, ed. 7, Philadelphia, J. B. Lippincott Company, 1949, p. 749.

study by Foote and Stewart [73] showed that only a minute fraction of the total number of intraductal papillomas become cancerous. This observation was also made in a series of 53 cases studied by Schie.[74] Anderson [75] said that a very small percentage of such lesions become papillary adenocarcinomas.

There is, however, one very important difference between hidradenoma of the vulva and intraductal papilloma of the breast. The latter is practically always multiple. Thus it seems improbable that one can invoke the idea of a developmental anomaly in such cases.

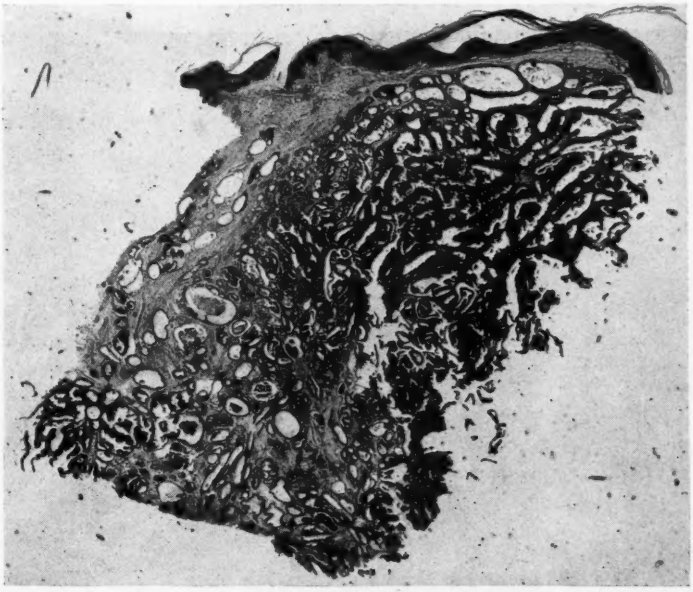

Fig. 5.—Low power view of a hidradenoma of the nipple with papillary adenomatous structure in the upper right portion and both apocrine and eccrine sweat glands in the lower left portion.

DIFFERENTIAL DIAGNOSIS

Metastatic Carcinoma of the Vulva.—In the differential diagnosis metastatic carcinoma of the vulva must be considered. According to

73. Foote, F. W., and Stewart, F. W.: Comparative Studies of Cancerous Versus Noncancerous Breasts, Ann. Surg. **121**:6 (Jan.) 1945.

74. Schie, E.: On the Prognosis of the Papilloma of the Lactiferous Ducts, Acta chir. Scandinav. **87**:417, 1942.

75. Anderson, W. A. D.: Pathology, St. Louis, C. V. Mosby Company, 1948, p. 1186.

Teacher [54] such lesions are not too uncommon. They may occur from hematogenous or lymphatic spread or by implantation from malignant lesions in the higher parts of the genital or urinary tract. Blood-borne metastases of the vulva have been found in association with hypernephroma, chorionepithelioma and adenocarcinoma of the uterus. Retrograde lymphatic spread may occur in carcinoma of the cervix. Actually, hidradenoma of the vulva must be differentiated histologically from metastatic lesions of adenocarcinoma of the cervix.[36]

Pyogenic Granuloma.—In one of our cases as well as in a number of the reported examples of this disorder there were many clinical similar-

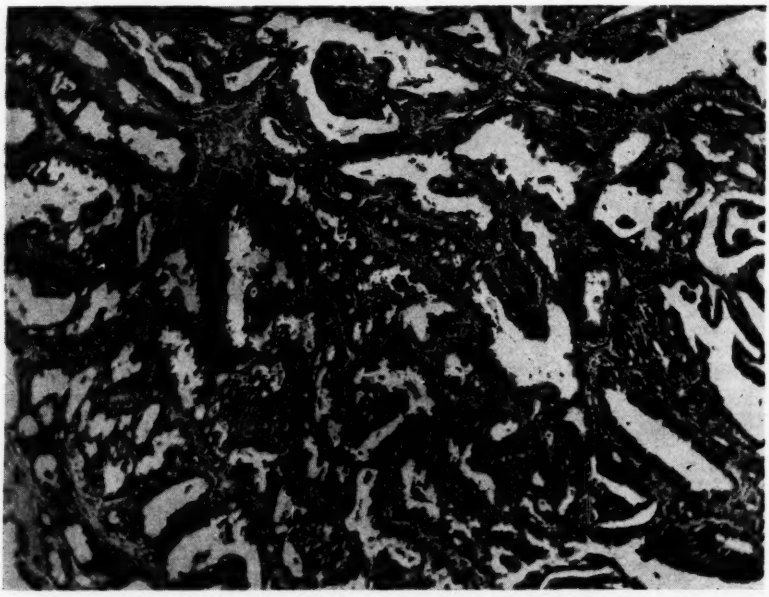

Fig. 6.—High power view of figure 5, showing cystadenomatous structure.

ities to pyogenic granuloma. These similarities include the fact that hidradenoma is usually a solitary lesion, it may erode the overlying epithelium and extrude its mass through such an opening, forming a raspberry-like lesion with a broad based pedicle, and, finally, it may bleed easily with trauma, although usually the bleeding is not profuse. Incidentally, pyogenic granulomas of the vulva occur, although they are rarely reported.[76]

76. Arnold, J.: A "Telangiectatic Granuloma" of the Vulva, Zentralbl. f. Gynäk. **54**:1189 (May 10) 1930; abstracted, Am. J. Cancer **15**:487, 1931. Isbruch, F.: A "Telangiectatic Granuloma" of the Vulva, Zentralbl. f. Gynäk. **53**:1579, 1929.

Sebaceous Cyst.—Because most hidradenomas do not erode the surface and because they remain as solitary subcutaneous lesions, they are often mistaken for sebaceous cysts. Failure to express a cheesy material after incision of a vulvar lesion should arouse one's suspicion of an erroneous diagnosis. Histologically, of course, such a differentiation causes no difficulty.

Accessory breast tissue in the labia majora might in rare circumstances be a cause of confusion.[77]

CONFUSION IN THE LITERATURE

There has been much confusion in the literature regarding these lesions. Thus case 2 of Eberhard and Warren [78] was a typical hidradenoma of the vulva both clinically and histologically but was described as a mucous gland tumor. Their first case was probably carcinomatous degeneration of a hidradenoma.

Hunt [79] did not mention hidradenoma of the vulva in the first edition of her book. However, in the second edition, on page 127 under the classification of malignant neoplasms, she mentioned sweat gland tumors of the vulva and stated that the microscopic appearance as well as the clinical manifestations are like those of a basal cell epithelioma.

Teacher [54] presented a typical hidradenoma of the vulva in his figure 307, terming it a papillary cystadenoma, and in the text said that these lesions occur as small tumors in the labium minus and labium majus associated with sebaceous [*sic*] or with Bartholin's glands. He then dealt separately with hidradenoma arising from sweat glands and said that the tumors may be single or multiple, appearing over the mons veneris and labia majora. Finally he stated that "Pick described the development of true adenocarcinoma in 3 of the 30 cases he investigated." I have not been able to confirm the latter statement.

FUTURE INVESTIGATIONS

Ordinarily each investigator feels that his contribution constitutes the last word on the subject. I feel that this is certainly far from true with regard to the condition under discussion. In the future investigations of sweat gland tumors of all types, particularly hidradenomas of the vulva and nevus syringocystadenomatosus papilliferus, it would seem worth while to consider certain procedures which might add to our limited knowledge of these conditions. First, there is the possibility in selected

77. Purves, R., and Hadley, J. A.: Accessory Breasts in the Labia Majora, Brit. J. Surg. **15**:279 (Oct.) 1927.

78. Eberhard, T. P., and Warren, S.: Mucous Gland Tumors of the Female Perineum, Am. J. Cancer **23**:334, 1935.

79. Hunt, E.: Diseases Affecting the Vulva, ed. 1, St. Louis, C. V. Mosby Company, 1940; ed. 2, London, Henry Kimpton, 1947.

cases of nevus syringocystadenomatosus papilliferus of careful microscopic and chemical examination of the secretion fluid. This would have been possible with the patient of Marcus and Wooldridge,[55] whose lesion discharged a small amount of milky fluid from a previously treated portion. It might also have been possible to make a chemical and microscopic examination of the secretion in Appel's [80] patient. Possibly some apparatus similar to that used by Lobitz and Osterberg [81] in their classic studies on sweat secretion would be of use.

Second, the possibility of using some intravital stains introduced into the tissues previous to biopsy might be explored. Third, special staining methods, such as the one for iron, might be employed. Homma,[82] as well as Way and Memmesheimer,[48] demonstrated the presence of iron in the secreting cells of the axillary apocrine glands and its absence in ordinary sweat glands. However, when iron is present it is not necessarily present in all the secreting cells of an apocrine gland (personal observation). Only 66 per cent of white persons and 70 per cent of Negroes had positive iron stains in Homma's investigation of apocrine glands. The failure of Biberstein [83] to find iron in nevus syringocystadenomatosus papilliferus cannot therefore be taken as excluding an apocrine gland or duct origin.

Finally, special silver impregnation stains might be employed as used by Hamperl [84] in the study of the myoepithelial elements of the mammary glands. Beerman [85] attempted without success to demonstrate these (method not stated) in a case of nevus syringocystadenomatosus papilliferus. Kuzma [86] suggested the use of Bouin's fluid as a fixative for 12 to 18 hours followed by the use of 80 per cent alcohol. In addition to ordinary hematoxylin and eosin staining, both van Gieson's stain and Masson's erythrosaffron can be employed for the identification of myoepithelial cells.

CONCLUSIONS

Hidradenoma of the vulva is a relatively rare condition and presents a characteristic clinical appearance and microscopic structure.

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80. Appel, B.: Nevus Syringadenomatosus Papilliferus, Arch. Dermat. & Syph. **61**:311 (Feb.) 1950.

81. Lobitz, W. C., and Osterberg, A. E.: Chemistry of Palmar Sweat: Preliminary Report; Apparatus and Technics, J. Invest. Dermat. **6**:63 (Feb.) 1945.

82. Homma, H.: On Apocrine Sweat Glands in White and Negro Men and Women, Bull. Johns Hopkins Hosp. **38**:365 (May) 1926.

83. Biberstein, H.: Syringocystadenoma Papilliferus, Arch. f. Dermat. u. Syph. **152**:602, 1926.

84. Hamperl, H.: The Myothelien (Myo-Epithelial Elements) of the Mammary Glands, Virchow's Arch. f. path. Anat. **305**:171, 1939.

85. Beerman, H.: Hypertrophic Darier's Disease and Nevus Syringocystadenomatosus Papilliferus, Arch. Dermat. & Syph. **60**:500 (Oct.) 1949.

86. Kuzma, J. F.: Myoepithelial Proliferations in the Human Breast, Am. J. Path. **19**:473, 1943.

In most cases it probably originates from the apocrine sweat glands, and hence identical lesions have been noted in the perianal region and the breast.

There is some relationship, at least histologically, beween hidradenoma and nevus syringocystadenomatosus papilliferus.

In spite of many excellent publications there is still great confusion as to the exact status of all types of lesions arising from both eccrine and apocrine types of sweat glands.

Further investigation of these interesting conditions is indicated.

ADDENDUM.—Since this paper was written Watkins and McDonald have published an article of considerable value to those who are interested in sweat gland pathology.[87]

ABSTRACT OF DISCUSSION

DR. L. H. WINER, Beverly Hills, Calif.: I wish to congratulate Dr. Anderson on his interesting and stimulating paper. It not only calls to the attention of the dermatologist the normal, the adenomatous and the neoplastic formations in apocrine and eccrine sweat glands but also stimulates speculation on the histogenesis of these lesions.

It is not difficult to differentiate the normal eccrine from the normal apocrine gland, but proliferations of these structures, especially when they consist of undifferentiated cellular formations, give no indication of the source of the tumor matrix or its epidermal primordium. This fact accounts for the reporting of what appears to be metaplasia or the change of one type of gland to another.

It is possible for the two types of cellular components of these glands to proliferate independently; proliferation of the secretory cells results in the formation of hidradenoma papilliferum and syringocystadenoma papilliferum (nevus syringocystadenomatosus papilliferus). Proliferation of myoepithelial cells produces a myoepithelioma. Secretory cells are not found in the ductal portion of the gland. I have on several occasions observed vacuolated cellular proliferation of the glandular portion and simultaneous solid cellular thickening of the ducts of these glands.

I consider both hidradenoma papilliferum and syringocystadenoma papilliferum as originating from the glandular portion of the apocrine gland. Hidradenoma occurs in a mature, fully developed apocrine gland which has reached its normal anatomic site, while the syringocystadenoma papilliferum (nevus syringocystadenomatosus papilliferus) develops in the epidermal primordial rest of the glandular portion of an apocrine gland which in its embryonic state had failed to penetrate down into the lower part of the cutis and into the subcutis. The latter lesion is an embryonic malformation of apocrine gland elements which remained at the embryonic site.

The borderline bewteen adenomatous and neoplastic proliferation of an apocrine gland is as indefinite as is the distinction between an adenoma of apocrine gland origin and a congenital malformation. W. C. Cooper and J. R. McDonald stated that hidradenomas are the only neoplasmas occurring in apocrine glands and that they very rarely become carcinomatous.

87. Watkins, D. H., and McDonald, J. R.: Surgical Significance of Sweat Gland Lesions of the Breast, Arch. Surg. **61**:610 (Oct.) 1950.

The above mentioned authors also reported a case of perianal localization of a hidradenoma of apocrine gland origin. Most authors have agreed that intraductal papillomas of the breast are closely related to hidradenomas, both histologically and histogenetically, and it is not unusual for a dermatologist to diagnose an intraductal papilloma of the breast as syringocystadenoma papilliferum.

In the differential diagnosis of sweat gland tumors one should always consider the highly malignant and rapidly fatal synovioma, which at times has been confused histologically with a sweat gland tumor. The stain for mucin is positive in synovioma. That lesion may further be identified by its biphasic morphologic picture, consisting of what appears to be epithelial and connective tissue proliferating side by side throughout the tumor. In some foci these different-appearing tissues can be seen to blend into each other, and at these sites they become monomorphous.

DR. NELSON PAUL ANDERSON, Los Angeles: I wish to thank Dr. Winer for his discussion. The question of metaplasia does arise. This has been reported in various abnormalities of the sweat glands and tumors of the sweat glands. Whether this is a factor here is rather doubtful. There are two or three points which I should like to emphasize. One is that, though in the average case it is easy to differentiate apocrine and eccrine sweat glands, there are cases in which it is extremely difficult. Secondly, while we are all in the habit of saying that apocrine sweat glands are found only in the axilla, about the breast and on the external genitalia of the female there is no doubt that isolated apocrine sweat glands occur elsewhere.

There is one additional point which I should like to make note of at this time even though it is in the paper: As one who has read considerably on this and other subjects I have always been impressed by the fact that when somebody finishes a presentation he seems to feel that the last word has been said. I have made a few suggestions in this paper for future investigations of such sweat gland lesions along lines which I feel are important. Included are certain suggestions such as the one that there be chemical and microscopic examination of the secreted fluid from some of these lesions, such as syringocystadenoma papilliferum. I think that the injection of some sort of stain before biopsy is performed might also be considered, as well as the use of special stains, such as that for iron, which, as you know, occurs in the apocrine glands and not in the eccrine group although iron is present only 60 to 75 per cent of the time in the apocrine group.

Finally, those who have studied the myoepithelium a great deal more than I stated that when one removes such lesions he should fix them in Bouin's solution for 14 to 18 hours and then with 80 per cent alcohol. Special stains such as erythrosaffron and van Gieson's stains as well as silver impregnation studies should then be employed. I think that in all types of papers suggestions for future investigations could be made. These might go a long way toward making a smoother path for another person who may be working on the same problem.

2007 Wilshire Boulevard (5).

MULTIPLE GLOMUS TUMORS

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REPORTS of glomus tumors have appeared in the literature with increasing frequency since this entity was described by Masson [1] in 1924. The vast majority of these cases reported have been concerned with small solitary tumors situated on an extremity which were characteristically extremely sensitive to slightest pressure. Even with increased awareness of this entity, it is still relatively rare. Love [2] in 1935 described the first glomus tumor recognized at the Mayo Clinic. He recently reported 13 more such tumors and stated that other tumors not included in his series had been diagnosed in the Clinic.[3] In the Section on Dermatology at the Clinic a histological and clinical diagnosis of glomus tumor has been made in nine additional cases, only one of which presented multiple glomus tumors. A survey of the literature revealed only 18 cases of multiple glomus tumors previously reported.[4] In one case reported by Weidman and Wise [5] 48 tumors were found; all other authors reported cases in which eight tumors or less were presented.

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* From the Section on Dermatology and Syphilology, Mayo Clinic.

Abstract, with additions, of thesis submitted by Dr. Eyster to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

1. Masson, P.; cited by Bailey: Am. J. Path. **11**:915, 1935.

2. Love, J. G.: Glomus Tumors: Diagnosis and Treatment, Proc. Staff Meet., Mayo Clin. **19**:113-116 (March 8) 1944.

3. Meyerding, H. W., and Varney, J. H.: Glomus Tumors: Report of 2 Cases, Minnesota Med. **30**:159-160 (Feb.) 1947. Love, J. G.: Glomus Tumors, ibid. **32**:275-277 (March) 1949.

4. (*a*) Slepyan, A. H.: Multiple Painful and Painless Glomus Tumors, Arch. Dermat. & Syph. **50**:179-182 (Sept.) 1944. (*b*) Beaton, L. E., and Davis, L.: Glomus Tumor: Report of 3 Cases; Analysis of 271 Recorded Cases, Quart. Bull., Northwestern Univ. M. School **15**:245-254, 1941. (*c*) Frykholm, R.: Deeply Situated Multiple Glomus Tumors: Case Report, Acta chir. Scandinav. **92**:368-376, 1945.

5. Weidman, F. D., and Wise, F.: Multiple Glomus Tumors of the Order of Telangiectases, Arch. Dermat. & Syph. **35**:414-426 (March) 1937.

Our report is of a case presenting 90 widely distributed tumors of the skin showing a histological structure compatible with Masson's original description but clinically similar to glomus tumors on the order of telangiectasias as described by Weidman and Wise.[5]

The normal glomus, according to Popoff,[6] is a modified arteriovenous anastomosis situated in the deep layers of the corium or in the stratum reticulare. It is composed of the arteriovenous anastomosis proper, the Sucquet-Hoyer canals, the outer laminated collagenous tissue and the primary collecting veins. The cytological make-up of the glomus is primarily distinguished by the presence of epithelioid or "glomus" cells. These cells are large polyhedral cells with clear or slightly granular eosinophilic cytoplasm and large slightly oval nuclei containing abundant chromatin. Bailey [7] stated that glomus tumors are widely distributed but are chiefly on the extremities and most abundant on the bed of the nails. They are imperfectly formed at birth, reach maximum development at young adulthood and subsequently atrophy in old age.

REPORT OF A CASE

A white woman 55 years of age was admitted to the Clinic with a chief complaint of swelling of her right arm. The skin lesions were concomitant observations. The duration of the swelling of her arm was 19 years, and the condition had begun with unexplained axillary adenopathy leading to multiple surgical procedures, including wide dissection of the axillas. The pathological process was reported as nonmalignant.

The first skin lesion noted was a bluish nodule near the outer canthus of the left eye appearing when the patient was about 15 years of age. It was not painful and had not enlarged appreciably since its first appearance. The second nodule appeared on the right forearm. This also was painless. In the intervening years similar nodules appeared on all parts of the body (fig. 1). The lesions appeared without known cause and remained symptomless unless traumatized. Only two lesions had been persistently painful since their appearance. One was situated on the ventral surface and the second on the dorsal surface of the right forearm. The first was extremely tender to pressure, and the second, sensitive only to deep pressure. The pain in both lesions remained localized, was associated with no vasomotor phenomena, was not influenced by changes of temperature and did not give rise to systemic reactions.

The patient reported that her mother had several similar lesions on her face and that her son also had several bluish nodules on his face. There was no opportunity to examine either.

Physical examination revealed lymphedema, grade 1 (on the basis of 1 to 4 with grade 1 representing the least degree and grade 4 the greatest degree) of the right arm and a diffuse nontoxic adenomatous goiter. Examination of the skin

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6. Popoff, N. W.: The Digital Vascular System, with Reference to the State of Glomus in Inflammation, Arteriosclerotic Gangrene, Diabetic Gangrene, Thromboangitis Obliterans and Supernumerary Digits in Man, Arch. Path. **18**:295-330 (Sept.) 1934.

7. Bailey, O. T.: The Cutaneous Glomus and Its Tumors—Glomangiomas, Am. J. Path. **11**:915-935 (Nov.) 1935.

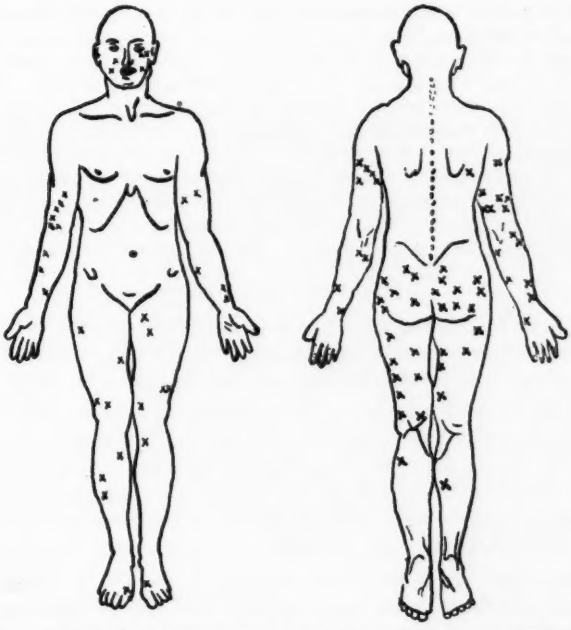

Fig. 1.—Sites of the glomus tumors in the reported case are indicated by *X*'s.

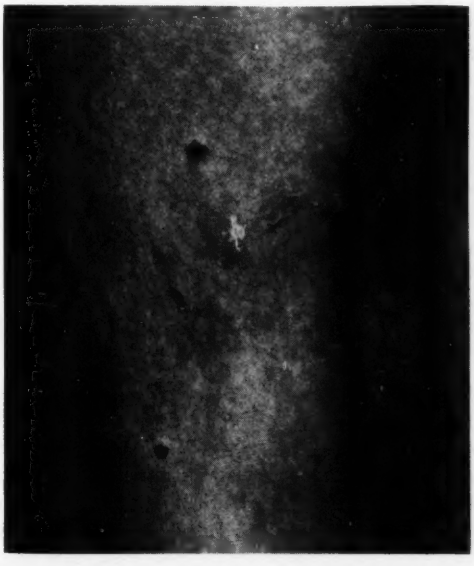

Fig. 2.—Typical skin lesions on the anterior portion of the right thigh.

revealed 90 nodules which were remarkably similar, discrete and sharply defined and which varied from 1.5 to 7 mm. in diameter in all gradations of color from blue to purple. The majority of the larger lesions were domed and slightly elevated above the surface of the skin (fig. 2). Some lesions appeared to be situated deeper in the cutis than others and had less sharply defined outlines. The skin over the lesions showed no apparent change. All lesions were easily compressed and gave no evidence of induration or infiltration. They blanched on diascopic pressure, but all color did not disappear. The extremely sensitive lesion on the ventral surface of the right arm was distinctly different from all other lesions. It was 3.5 cm. in its longest diameter and 2 cm. in its least diameter. It lay deep in the corium, was not elevated above the skin, was deep blue and had indistinct outlines.

MICROSCOPIC EXAMINATION

Three representative lesions were excised, two painless tumors from the dorsal surface and the painful lesion on the ventral surface of the right forearm. The epidermis was within normal limits in all tumors, as were the dermal appendages. The pathological picture for the painless tumors was confined to a circumscribed but nonencapsulated lesion lying at the junction of the corium and the subepidermal fat (fig. 3 *a*). The lesions consisted of anastomosing irregular blood spaces separated by collagenous tissue. Three types of blood spaces were seen: 1. There were thin-walled, endothelum-lined and voluminous spaces situated chiefly on the side of the lesion nearest the epidermis. These spaces contained abundant elastic tissue in their walls but no epithelioid cells. 2. Spaces of the second type conformed to the description of Sucquet-Hoyer canals in that they lacked elastic tissue and their walls were composed of endothelium and smooth muscle cells intermingled with the epithelioid cells. 3. The predominating type consisted of irregular, cavernous, anastomosing blood spaces with walls of varying composition. Some showed definite endothelium with underlying epithelioid cells, but the walls of the majority were composed chiefly of epithelioid cells in one, two and sometimes many layers. In places masses of these epithelioid cells pushed into the lumen of the vascular spaces to make a cushion of cells.

The epithelioid cells mentioned in the preceding paragraph were large cells with clear or slightly granular eosinophilic-staining cytoplasm of indistinct outline which were packed closely into the wall of the blood spaces. The nuclei were large and oval and contained much chromatin. There was little variation of these cells. No mitotic figures were seen (fig. 3 *b*).

Bodian stain revealed the presence of fine neurofibrils which were almost always in close association with the vascular spaces of the Sucquet-Hoyer type in all the tumors examined. Elastin H stain revealed a well defined lamina of elastic tissue in the thin-walled peripheral spaces which did not contain epithelioid cells. It demonstrated an elastic tissue lamina in the thick-walled central vessel, which was then

interpreted as the afferent arteriole. The majority of the vascular spaces, and especially those characterized by an excess of epithelioid cells, were lacking in elastic tissue. Van Gieson's stain demonstrated that the tissue

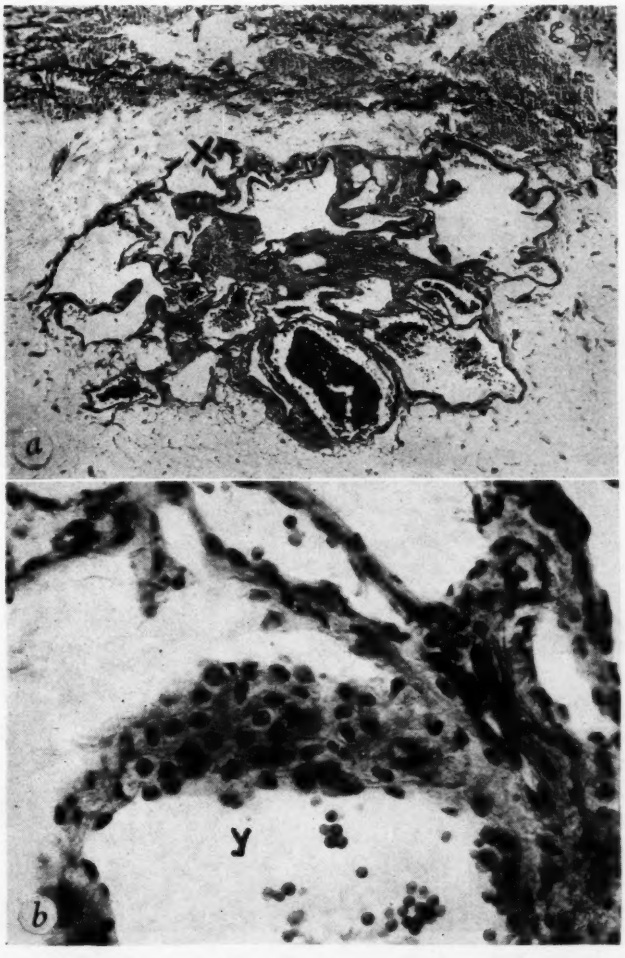

Fig. 3.—(*a*) Painless tumor at the subcutaneous-cutaneous junction showing vascular structure and a cushion of epithelioid cells at *X*, hematoxylin and eosin, × 26. (*b*) High power view of cushion of epithelioid cells lining a vascular space, *Y*; hematoxylin and eosin, × 430.

between the vascular spaces was a delicate reticulum of collagenous tissue. There was no collagenous capsule.

Neurofibrils were demonstrated in the majority of the sections of the painful tumor stained with Bodian stain. They were associated intimately with the epithelioid cells, typically in an area in which the

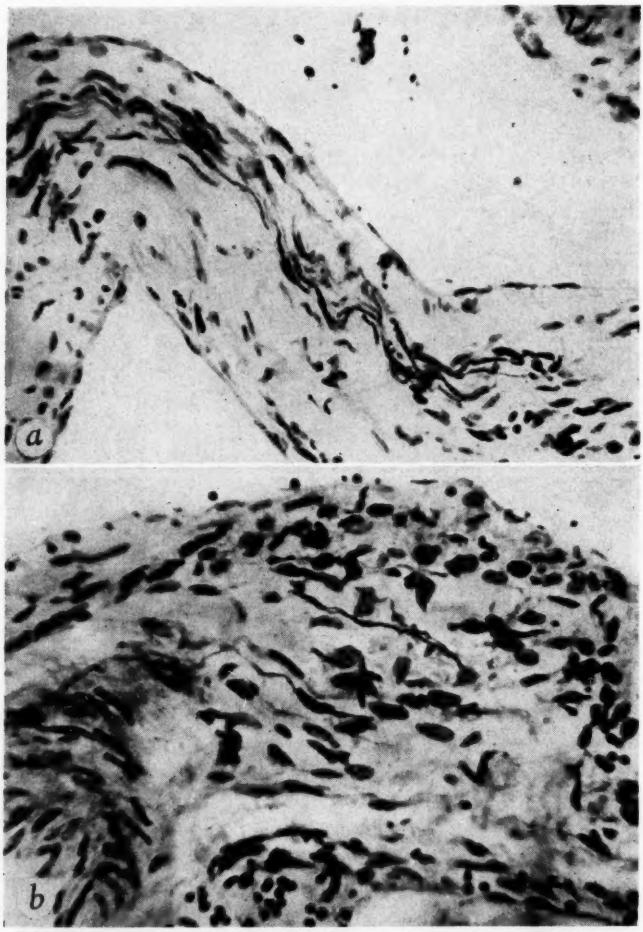

Fig. 4.—(*a*) Neurofibrils stained black in a painless tumor; Bodian stain, × 440. (*b*) Similar unmyelinated neurofibrils in a painful tumor; Bodian stain, × 440.

cells formed a cushion that projected into the lumen of the vascular space (fig. 4). The vascular space almost invariably was one of the type similar to the Sucquet-Hoyer canals. The neurofibrils in the pain-

less lesion were sparse and were found only after prolonged search of numerous sections. Again, they were found associated with the vascular

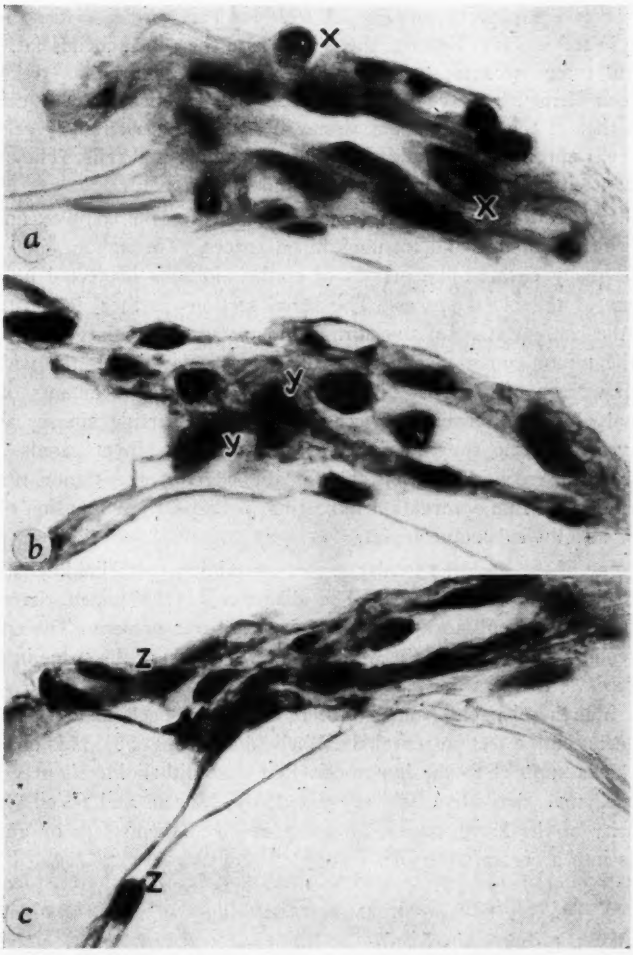

Fig. 5.—Consecutive serial sections of the termination of a vascular space. Note (*a*) large epithelioid cells in the wall of the space at *X* (hematoxylin and eosin, × 1,160), (*b*) transitional forms at *Y* (hematoxylin and eosin, × 1,130) and (*c*) undifferentiated mesenchymal cells surrounding the terminal vascular space at *Z* (hematoxylin and eosin, × 950).

spaces most nearly resembling normal Sucquet-Hoyer canals. With the aforementioned stains the only essential observable differences between

the painful and painless tumors were that neurofibrils were demonstrated much more easily in the painful tumor and that the painless lesions were circumscribed and compact.

The two painless tumors excised were compact, circumscribed tumors lying in the junction between the corium and the subcutaneous fat. The painful tumor was much more diffuse, with a collagenous reticulum between elements of the vascular spaces. This reticulum was distinct from that of the subcutaneous tissue in that it was extremely cellular. The cells appeared to be undifferentiated mesenchymal cells. They were stellate, with large oval nuclei and abundant chromatin.

Serial sections were made. They demonstrated the complex anastomosis of the dilated and tortuous blood spaces. Throughout the entire tumor many cushion-like masses of epithelioid cells projected into the lumens of the blood spaces. The serial sections further demonstrated that the configuration of the normal glomus was, to a large part, lost, for the tumor consisted chiefly of dilated vascular spaces the walls of which were composed of epithelioid cells. The only remnants of the normal glomus discoverable were the venous collecting sinuses and a few vessels fitting the description of the Sucquet-Hoyer canals. The venous sinuses were concentrated at the edge of the tumor nearest the epidermis, this observation indicating, perhaps, the expansion of the tumor into the subcutaneous fat.

Some of the typical vascular spaces containing epithelioid cells were traced to their terminations. The diameter of the lumen decreased irregularly until only a capillary-like structure was present. The epithelioid cells were present in the walls until termination of the space in some instances. In others the terminal space was surrounded by cells which were indistinguishable from undifferentiated mesenchymal cells. The next consecutive section revealed epithelioid cells (fig. 5). This observation lends support to the hypothesis that the epithelioid cell may be a mesenchymal derivative, as suggested by Mason and Weil.[8] The majority of the blood spaces, however, resolved themselves by anastomoses into a central arteriole.

NORMAL GLOMUS

Knowledge of the structure of the normal glomus is essential in a discussion of glomus tumors. Popoff [6] emphasized that the glomus body is a modified arteriovenous anastomosis. The anastomotic unit includes the afferent artery, one to four Sucquet-Hoyer canals, the neuroreticular and vascular structures around the Sucquet-Hoyer canals, the

8. Mason, M. L., and Weil, A.: Tumor of a Subcutaneous Glomus, Surg., Gynec. & Obst. **58**:807-816 (May) 1934.

outer laminated collagenous tissue and the primary collecting veins. The afferent artery is found to be a branch of the arteriole which arises from the subcutaneous arteriolar network and supplies the papillary bodies. The glomus branch comes off at the level of the stratum reticulare. The afferent artery breaks up into one to four Sucquet-Hoyer canals. At the point of its branching there is a distinct collagenous ruffle with an elastic lamina under the endothelium. This point is the termination of the elastic lamina, for the Sucquet-Hoyer canals are characterized by the absence of an elastic lamina. The Sucquet-Hoyer canals consist of an endothelium surrounded by a thick muscular coat with indistinct inner longitudinal and outer circular layers. Among the muscle cells are large cells with clear or vacuolated cytoplasm which do not contain stainable glycogen, fat or mucin but which have slightly elongated polyhedral nuclei. The muscular coat is surrounded by a wide zone of delicate collagenous reticulum with a rich network of nonmyelinated neurofibrils in close proximity to the walls of the Sucquet-Hoyer canals. The efferent portion of the anastomosis is characterized by thin walls, few muscle cells, abundant elastic tissue and disappearance of the clear neuroreticular zone. The collecting veins have the shape of a broad ruffle or cape surrounding the glomus and form a voluminous receptaculum. The entire glomus is surrounded by coarse laminated collagenous tissue.

GLOMUS TUMORS

The glomus tumors heretofore described have fallen into two types, both characterized by a histological picture of contorted, dilated vessels with walls containing the epithelioid cell and usually more specialized vessels similar to the normal Sucquet-Hoyer canals. One type of glomus tumor, as described by Bailey,[7] was characterized by pain, was deep red to purple, was sharply demarcated and presented no erosion of the skin. Histologically it presented contorted vessels with peculiar walls. As indicated earlier, the vessels of this tumor presented two kinds of structure. In one the vascular spaces were surrounded by smooth muscle cells which were in turn surrounded by shorter, larger cells with clear or pale-staining cytoplasm and compact nuclei. The latter cells blended with the typical polygonal glomus cells. The second type of vascular space was the same as those previously described except that the smooth muscle cells were absent. This type of glomus tumor was distinguished by neurofibrils in close association with the walls of the blood spaces and intermingled with the glomus cells.

The second type of glomus tumor was described by Weidman and Wise.[5] Tumors of this type were multiple, 48 being found in one case, painless and characterized by a histological structure consisting of irregular cavernous blood spaces with a mantle of epithelioid cells. These mantles were one or two layers thick in some places, and in other places

the cells were piled up in large lobulated masses. Small clumps of involuntary muscle fibers were present but no neurofibrils. The lack of pain and the lack of neurofibrils in histological section distinguished this type of tumor.

Opinions are distinctly divided on the question of whether or not pain and neurofibrils must be present to validate the diagnosis of glomus tumor. Masson,[1] in his original description of glomus tumor, presented the triad of histopathological findings of increase in epithelioid cells, vascular spaces (either with or without muscle cells) and neurofibrils in association with the epithelioid cells. These three histopathological observations were also given by Popoff [6] in his work on glomus tumor. Bailey [7] concurred in his presentation of glomangiomas, a term he preferred to glomus tumor. The vast majority of case presentations and discussions of glomus tumors have followed the tenets of these three authors in the identification of glomus tumors. Weidman and Wise expressed the opinion that the presence of epithelioid cells and elements of smooth muscle in a circumscribed vascular tumor located in the stratum reticulare and abutting on the subcutaneous fat fulfilled enough of the criteria as laid down by Masson to establish a diagnosis of glomus tumor. They felt that their case, in which neurofibrils were not demonstrable, should be classed thus. Love and Kernohan [9] were not impressed with a rich neural connection in their discussion of glomus tumors. Alvarez Cascos and Costero [10] expressed an opinion that neural elements do not form an integral part of the tumor tissue but are normal neural fibers which happened to get tangled in the tumor. Other authors have described cases of nonpainful as well as painful tumors in the same case with a histological picture identical in both types of tumors except that the nonpainful lesions lacked neurofibrils in their structure.[11]

The origin of the pathognomonic epithelioid or glomus cell has been another point which has produced a difference of opinion, although all authors have agreed that the cell is unique to the glomus body and to glomus tumors. Popoff, in his classic study of the digital vascular system, expressed an opinion that the epithelioid cell is not truly a separate cell but a smooth muscle cell with voluminous cytoplasm cut transversely. Murray and Stout,[12] in their studies of tissue culture of glomus tissue,

9. Love, J. G., and Kernohan, J. W.: Glomangioma or Glomus Tumors, in Allen, E. V.; Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, W. B. Saunders Company, 1946, chap. 23, pp. 562-570.

10. Alvarez Cascos, M., and Costero, I., cited by Mason and Weil.[8]

11. Slepyan.[4a] Adair, F. E.: Glomus Tumor: A Clinical Study with a Report of 10 Cases, Am. J. Surg. **25**:1-6 (July) 1934.

12. Murray, M. R., and Stout, A. P.: The Glomus Tumor: Investigation of Its Distribution and Behavior, and the Identity of Its "Epithelioid" Cell, Am. J. Path. **18**:183-203 (March) 1942.

considered the epithelioid cell a modified smooth muscle cell. They described the glomus cell as it progressed through a regular series of transitional forms. In spite of its persistent absence of myofibrils, they observed its contractility and concluded that its function was to occlude the glomus vessel and that it therefore should be classed as a modified smooth muscle cell. They further concluded that this cell was the same cell as that described by Zimmerman [13] in 1923 as a pericyte, because both the glomus cell which they had observed and the pericyte observed by Zimmerman were in the same position in relation to the vessel, had the same function and assumed the same form when not crowded as in vivo. Zimmerman observed that the capillaries were encircled with a special kind of cell, extending in both directions, toward the arteries and toward the veins, which gradually passed through transitional forms into smooth muscle fibers. These cells were contractile and acted to regulate the flow of blood in the capillaries. There was no nerve associated with either the glomus cell studied by Murray and Stout or the pericyte of Zimmerman. Clark and Clark,[14] in their observations of arteriovenous anastomoses in a "round table" chamber in a rabbit's ears, stated that the walls of new capillaries are composed of endothelial cells, with the addition soon after of longitudinally placed adventitial cells. They observed the formation of these adventitial cells from wandering fibroblasts. In the arterial portion of the anastomoses these adventitial cells were replaced by smooth muscle cells, but Clark and Clark were not able to determine whether this change was a result of a transformation of the adventitial cells or whether some other mechanism was operating. These cells showed contractility and were in the same relationship to the blood vessel as the pericytes of Zimmerman and the glomus cells. Murray and Stout expressed the opinion that these adventitial cells of Clark and Clark are probably identical with the glomus cells.

Krompecher,[15] in his studies of serial sections of the glomus coccygeum of the human fetus, newborn baby and infants, expressed the conclusion that the epithelioid cells arise from embryonic rests of angioblasts and are mesenchymal derivatives which have advanced to the stage of elastoblasts. Alvarez Cascos and Costero [10] stated the opinion that glomus tumors are of vascular and epithelial origin.

COMMENT

Our case fulfils all criteria necessary for the diagnosis of glomus tumor and yet is unique in that there are 90 such tumors on all parts

13. Zimmerman, K. W., cited by Murray and Stout.[12]

14. Clark, E. R., and Clark, E. L.: The New Formation of Arterio-Venous Anastomoses in the Rabbit's Ear, Am. J. Anat. **55**:407-467 (Nov.) 1934.

15. Krompecher, S.: Histologische und entwicklungsgeschichtliche Untersuchungen über das Glomus coccygeum des Menschen, Verhandl. d. anat. Gesellsch. **41**:176-185, 1932.

of the body. Clinically the lesions caused so little discomfort that they were of secondary importance, for the patient was more concerned about the edema of her right arm. Histologically the tumors were composed of dilated blood spaces the walls of which contained pathognomonic epithelioid cells. Some blood spaces were distorted out of all semblance to the Sucquet-Hoyer canals, but others still showed endothelium, intermingled smooth muscle cells and epithelioid cells and lacked an elastic tissue lamina. Collecting venous spaces which were distorted but recognizable were present. These were thin-walled endothelium-lined spaces with an elastic membrane which did not contain epithelioid cells. There was a thick-walled arteriole in the tumor which was seen to break up into the blood spaces containing epithelioid cells. There was a pronounced increase in the number of epithelioid cells. Neurofibrils were demonstrated by special stains in the tumor and were intimately associated with the epithelioid cells. The tumor, therefore, fulfilled the criteria of Masson,[1] Bailey [7] and Popoff [6] and should be classified as a glomus tumor. The case, however, bore a pronounced likeness to the one reported by Weidman and Wise in that the tumors were multiple, painless and widely distributed, with a histological picture of tortuous, dilated vessels chiefly of the type containing epithelioid cells.

Our case would therefore fit the description both of the classic glomus tumor and of the glomus tumor on the order of telangiectasia. It should serve to reconcile the differences of opinion on the classification of tumors showing all the essentials of a glomus tumor except painful symptoms and neurofibrils.

It seems logical to think that the pathogenesis of this tumor is a peculiar proliferation of the epithelioid elements in their vascular form so that when the tumor reaches macroscopic size the nonproliferating elements of the glomus body are decidedly reduced in their significance and comparative numbers. Thus any of the venous collecting spaces, the neurofibrils and even the Sucquet-Hoyer canals containing smooth muscle which are not affected are pushed aside. It should not be difficult to conceive that a section or several sections might miss entirely the nonproliferated elements which might have been revealed by serial sections.

Thorough study of serial sections of these tumors revealed that the terminations of some of the blood spaces containing epithelioid cells were surrounded by primitive cells arising in the mesenchymal tissue. Contiguous sections showed the presence of epithelioid cells and also cells that might be interpreted as transitional forms. This observation and the fact that an observable excess of epithelioid cells exists without a single mitotic figure would be compatible with the theory that the epithe-

lioid cell is a mesenchymal derivative. Maximow and Bloom [16] stated that many investigators agreed with Marchand [17] that some cells that retain the potencies of undifferentiated mesenchymal cells remain in the adult organism. These cells are frequently smaller than the fibroblasts but have the same general appearance. They are found in the loose connective tissue and are usually arranged along the blood vessels and especially along the capillaries. These cells have been thought to be undifferentiated mesenchymal cells, for numerous observations showed that under the influence of certain stimuli such as tissue culture, inflammation and the injection of blood toxins they might undergo progressive development and furnish new types of cells. Further, as new capillaries arose, they were seen to be accompanied with connective tissue cells and layers of thin collagenous or reticular fibers. The connective tissue cells were observed to consist of fixed macrophages, undifferentiated mesenchymal cells and a few scattered neural cells. It would seem logical, therefore, to ascribe the origin of epithelioid cells to these undifferentiated mesenchymal cells under the influence of stimuli not yet apparent, for these mesenchymal cells furnish the available source of the great number of epithelioid cells present in a situation where mitosis is lacking. Whether these same undifferentiated mesenchymal cells may develop into smooth muscle cells remains a moot question, although the observations of Clark and Clark would lend support to this hypothesis. Perhaps the soil determines whether the undifferentiated mesenchymal cell is differentiated into smooth muscle or into the epithelioid cell. That is, in the child the same cell, or different cells which are indistinguishable by present methods of investigation, may develop into the glomus cell or into the smooth muscle cell, respectively. On the other hand, in tissue of adult persons only the epithelioid cell develops, for glomus tumors are seen exclusively in adults and the proliferated elements are the epithelioid cells. Further, smooth muscle cells have been found only in the walls of the minority of the vessels, those which resembled the original Sucquet-Hoyer canals, this observation indicating a lack of proliferation of smooth muscle cells. Smooth muscle cells and epithelioid cells have not been found admixed haphazardly in the walls of the proliferated vascular spaces, as might be expected if the epithelioid cell were a transitional form between the mesenchymal cell and the smooth muscle cell or if the epithelioid cell and the smooth muscle cell developed from a common type of cell in the adult. If the epithelioid cell were a modification of the smooth muscle cell, that modification would have to be on the basis of the development of a mesenchymal cell into either a smooth muscle cell or an epithelioid cell

16. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 5, Philadelphia, W. B. Saunders Company, 1948.

17. Marchand, F., cited by Maximow and Bloom.[16]

in the child, for myoblasts contain definite granules which go to form the myofibrils.[18] Granules have not been observed in the epithelioid cells, and in an area of excess of one cell type transitional forms between the precursor cell and the cell type in question should be discoverable. Thus, the epithelioid cell is probably an independent specialized type of cell which develops from the undifferentiated mesenchymal cell in the peculiar environment of the glomus arteriovenous anastomosis and is related to smooth muscle only by its property of contractility and origin from mesenchymal tissue.

SUMMARY

A case is reported in which the patient presented 88 painless and two painful tumors having the histological structure of glomus tumors. This case is remarkable in two respects—first, because of the great number of tumors, and, second, because of the clinical similarity to the so-called tumors on the order of telangiectasia and the histological triad of observations which permit the lesions to be classified as glomus tumors. Thus, this case may represent a transitional form between the painless glomus tumors and the painful tumors, thereby resolving the discussion on that point. Study of serial sections revealed pronounced overgrowth of the elements of the epithelioid cell which tended to obscure the unproliferated glomus elements. Serial sections further revealed cellular components at the terminal phases of epithelioid cells containing vascular spaces, which would support the concept that the epithelioid cells are mesenchymal derivatives arising from the undifferentiated mesenchymal cells.

18. Jordon, H. E., and Kindred, J. E.: Textbook of Embryology, ed. 5, New York, D. Appleton-Century-Crofts Company, Inc., 1948.

Clinical Notes

CHLOROMYCETIN® FOR ECZEMA AND PRURITUS OF THE EAR CANAL

THEODORE CORNBLEET, M.D.
and
H. C. SCHORR, M.D.
CHICAGO

Itching with or without evident dermatitis of the ear canals is a common complaint. Like some other frequent disorders, such as the common cold, its cause is the subject of debate. The many forms of treatment recommended merely attest to the indifferent results following them.

Until the cause of the frequent ailment of itching and dermatitis of the ear canals is better known, it would seem just as well to apply an indifferent name, such as "eczema," to it. For a number of years, there has been a determined effort by some to eliminate the term "eczema" for varieties of dermatitis of the skin. These persons object to the use of the word as connoting some special type of dermatitis which, whatever its clinical distinctions, is not clearly reflected histologically. It is felt here, on the other hand, that the dermatitis of the ear canals should be labeled simply "eczema" for the opposite reason—doing so confesses ignorance as to cause and provides a reasonable enough definition of the entity. To say "dermatitis of the ear canals" simply implies inflammation, which is present in psoriasis, too, but yet is not eczema. This latter disease affects the external ear not uncommonly and, while it most frequently is seen also on other parts of the skin, confounds at times by being present only in the ears. Psoriasis is frequently differentiated with difficulty from seborrheic dermatitis. Both of these conditions in the ears are likely to be stubborn and long lasting. Occasionally one observes a dermatitis of the ears which yields only when its cause is found in some material, such as a cosmetic, to which the person has become hypersensitive. A large number of these eczemas of the ear canals have been classified as otomycosis because of the presence of various fungi.

In recent years there has been increasing doubt as to the pathogenicity of the various aspergilli, penicillia, mucors, yeasts and various fungi found associated with eczema of the ear canals. This has been counterbalanced by a growing belief that it is the bacteria found there that are more likely to be at fault. It is now commonly thought that fungi in the ear canals are harmless contaminants, growing easily on suitable soil present there. Until more is known about this malady, it seems better to abandon the term "otomycosis" for one which implies no definite cause.

In a group of persons studied, an effort was made at selecting those for whom a diagnosis of psoriasis, dermatitis venenata, pyogenic infection or middle ear infection could be excluded. There were thus 18 patients found who complained of itching of the ear canals and several who showed various degrees of inflammation of the parts. In four there was a dry scaling chronic dermatitis, and in three there was some moisture. In two the process was acute. Cultures were made in all cases, with results that have frequently been reported by others. A variety of fungi were grown, and, of the bacteria, streptococci were most commonly isolated.

From the Departments of Dermatology, University of Illinois College of Medicine and Cook County Hospital.

This group of patients was treated with an ointment made of chloramphenicol (chloromycetin®), 0.275 Gm. to the ounce (30 Gm.) of carbowax® 1500. The antibiotic rubs up easily and well in this base, and the latter is borne comfortably by the ear canal. It was previously found that this statement could not be made for petrolatum, which imparts an uncomfortable sense of fulness when on the ear drum. Carbowax® 1500 is said to have antipruritic qualities of its own, but used alone it gave no relief to any in this group of patients. The actual application of the medicament was found little of a problem. The material was entrusted to the patient himself, with the admonition not to apply it beyond the ostiums of the canals. A definite greasing of the entire circle constituting the end of the canal evidently sufficed to suffuse in time to the depths. Applications were made morning and night.

Of the 18 subjects so treated, all but two had a favorable and rapid response. Itching ceased early, and secretions dried. In two a thin membranous cast came away in shreds. Visible healing occupied from two to 14 days. In four cases there were recurrences of symptoms, which again responded promptly to application of the ointment. For them—and probably best for those where this malady is known to recur—it was advised that applications be made prophylactically twice a week.

In the culture made from one patient, a hemolytic Streptococcus appeared prominently. This organism was observed by the tube test using chloramphenicol in the high concentration of 1 to 5,000. The added antibiotic did not evidently restrain growth, although in ointment it was effective against the eczema in the ear canal.

In none of the patients did irritation follow the applications. Since it is known that some other antibiotics may induce sensitization in the form of dermatitis venenata, this was looked for. There is a common feeling among dermatologists that it is better to avoid the local use of medicaments which can sensitize and yet may be needed internally for some future emergency. The desirability of modifying this dictum in the case of chloramphenicol would seem to be suggested by its exceptional effectiveness in clearing an otherwise resistant and stubborn disease and its small capacity to sensitize locally.

SUMMARY

Eighteen patients with itching and eczema of the ear canals were treated with an ointment made with chloramphenicol and carbowax® 1500. Sixteen had an early and favorable response with no ill effects.

ADDENDUM.—In a follow-up inquiry, eight of the subjects could be found. Three of them said that the improvement in their condition had been only temporary and that the original condition of the ear canals had recurred despite the continued use of the ointment.

USE OF AUREOMYCIN OINTMENT IN SYCOSIS VULGARIS

Report of a Case

THOMAS S. SAUNDERS, M.D.
PORTLAND, ORE.

Sycosis vulgaris, as ordinarily encountered, is an extremely chronic disease characterized by an amazing measure of resistance to treatment. The following case history demonstrates a remarkable therapeutic result from the use of aureomycin ointment.

R. B., a man aged 24, stated that in 1945 he first acquired pustular lesions on the chest while serving in the armed forces in the tropics. He subsequently acquired lesions on the forearm and knees (nature unknown) which cleared up under roentgen ray treatment. In the fall of 1947 he first manifested lesions on the face which tended to clear up and recur. In the spring of 1948, over a four month period, he received four roentgen ray treatments to his face, took injections (vaccine?) and used salves with benefit. However, his lesions soon recurred, and he received additional roentgen ray treatments without benefit. In the summer of 1948 he applied penicillin ointment with remarkable benefit, but the continued use of penicillin ointment produced a reaction of redness and itching (contact dermatitis?).

When the patient was examined on Dec. 21, 1948, his chin and upper lip area were covered with follicular pustules and vegetative crusts. Bacitracin ointment was prescribed, with temporary benefit. Nitrofurazone (furacin®) ointment and quinolor® compound ointment (benzoyl peroxide, 10 per cent, and quinolor® [chlorhydroxyquinoline], 0.5 per cent, in a base of equal parts of white petrolatum and deodorized wool fat) were next prescribed without benefit. A culture of the pus on Jan. 31, 1949, showed numerous hemolytic Staphylococcus aureus which gave a positive reaction to the coagulase test in 45 minutes. No fungi were demonstrable on culture.

From January 31 to February 16 the patient was given eight roentgen ray treatments, according to the four point Kienböck technic for beard epilation. This therapy was followed by a satisfactory epilation and resolution of most of the inflammatory masses. Pronounced improvement resulted, but a honey-crusted area persisted on the chin. This area was given four additional roentgen ray treatments of 75 r each. A moderate degree of improvement followed. On May 4 the patient returned with an extensive (staphylococcic) blepharitis with a flare-up of the sycosis on the upper lip and chin area. Aureomycin drops were prescribed for the blepharitis and streptomycin ointment for the chin and upper lip condition. No conspicuous benefit appeared. On July 12 aureomycin ointment (30 mg. to each gram) was prescribed, and its use resulted in a dramatic improvement. On August 29 the patient's face was entirely clear for the first time in two years. It had remained so at the time of writing.

1020 South West Taylor Street.

PERLÈCHE FROM PENICILLIN DUST

LEONARD C. GREENFIELD, M.D.
CHICAGO

Perlèche is usually attributed to infection by streptococcic, staphylococcic or monilial organisms; to a deficiency of vitamin B, particularly riboflavin, or to maceration, as from an overhanging upper lip or excessive salivation. To this list should be added another causative factor, penicillin dust. While it has been noted that perlèche-like lesions may occur with the stomatitis that results occasionally from the use of penicillin troches,[1] it is not generally recognized that in susceptible

Northwestern University Medical School, Department of Dermatology.

1. Farrington, J.; Riley, K., and Olansky, S.: Untoward Reactions and Cutaneous Testing in Penicillin Therapy, South. M. J. **41**:614 (July) 1948. This article considers the pathogenesis and bacteriologic and mycologic changes that occur in stomatitis from penicillin.

persons perlèche may result from contact with the penicillin powder that is used for inhalation therapy.

The condition was called to my attention by Dr. L. B. Bernheimer, an otolaryngologist, who remarked that he had noted several such cases in persons who had used the new home type apparatus for such therapy, and I have since observed 10 other cases in the practice of Dr. Herbert Rattner. Perlèche from any cause is fairly common, but with the increasing popularity of inhalation therapy it is likely that more cases will be encountered. The condition, characterized by scaly, eroded, fissured or macerated lesions at the angles of the mouth, although not serious does cause some discomfort. In two of our cases there was also some redness of the tongue, and in three of them, punctate hemorrhages of the palate. In all the cases, when the use of penicillin was discontinued the condition showed immediate improvement and cleared completely with the use of a soothing protective cream.

ALOPECIA FROM HAIR STRAIGHTENING

JAMES W. ANDERSON, M.D.
NORFOLK, VA.

Dermatologists in the South and other areas with a large Negro population are seeing increasing numbers of a curious type of alopecia, which, for lack of a better term, I have been calling "hair straightener alopecia." As I was unable to find any reference to it in the literature, I thought it might be worth while to describe it.

Many Negroes are resorting to a hair-straightening process consisting in the application of a hair dressing followed by combing with a hot comb. A check on several brands of the dressing showed these preparations to be essentially a mixture of sodium hydroxide in some greasy base, usually petrolatum. This dressing is liberally applied to the hair and scalp, and then the hair receives a brisk combing with a heavy metal comb which has been heated to a rather high temperature.

A typical case of hair straightener alopecia consists in a variable area of baldness, sometimes extending to the middle of the scalp, in which stumps of broken hairs are visible. As the combing takes place from the front to the back, the baldness begins on the frontal area. There is a dry, seborrheic type of dermatitis on the bald area and usually on the remainder of the scalp. Frequently an area of depigmentation exists on the forehead, extending 2 to 3 cm. below the hair margin. Occasionally treatment dermatitis complicates the picture as a result of the use of some fungicide because of the impression that the condition is tinea.

The majority of patients are women, but an occasional man is seen who has attempted to produce a pompadour effect. As two factors are involved, the application of a caustic to soften the hair and the trauma from the heat and brisk combing, probably a combination of the two produces the alopecia.

No treatment is necessary, for on discontinuance of the hair-straightening process the hair rapidly returns.

Suite 303, Medical Arts Building (10).

TOPICAL USE OF NEOMYCIN

Preliminary Report

ROY L. KILE, M.D.
ASHTON L. WELSH, M.D.
and
GEORGE D. McAFEE, M.D.
CINCINNATI

The wide antibacterial spectrum of neomycin (derived from Streptomyces fradiae) prompted a decision to use it topically.

It was prepared in two ointment bases: one, water miscible, and the other, a greasy base.[1] The concentration used in the majority of cases was 5 mg. per gram.

The more than 200 patients who used these preparations had various pyogenic skin infections such as impetigo, sycosis and furunculosis. Infectious eczematoid dermatitis comprised another large group. In the majority of instances therapeutic results with neomycin have been superior to those with any preparation previously used.

To date, no case of irritation has been proved to be due to the neomycin. This series has included several patients known to be sensitive to penicillin, streptomycin, bacitracin and aureomycin applied topically. In several patients in whom irritation occurred, it was proved to be due to the ointment base used. Undoubtedly cases of sensitivity will be found, but apparently they will be rare.

Enthusiasm about any new drug is usual, but neomycin has been so effective and well tolerated that it is difficult to curb one's enthusiasm.

An extensive study is under way including bacteriologic studies and the accumulation of data on more cases for a complete subsequent report.

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1. Furnished by the Upjohn Company.

Society Transactions

NEW YORK DERMATOLOGICAL SOCIETY

Frank C. Combes, M.D., *President*
John C. Graham, M.D., *Secretary*
Feb. 15, 1949

Squamous Cell Epithelioma, Ten Years After Treatment. Presented by Dr. A. Benson Cannon.

R. M., a woman aged 42, is presented to show the results of treatment of an epithelioma 10 years ago. She was previously presented before this Society on Feb. 28, 1939 (Arch. Dermat. & Syph. **40**:510 [Sept.] 1939), with a squamous cell epithelioma located on the upper lip just below the angle of the nose. The lesion had been present for four weeks at that time. A biopsy report showed squamous cell epithelioma. The lesion was of interest because of the clinical resemblance to chancre. No enlarged glands were palpated. The patient had had radiotherapy for acne vulgaris 10 years previously. There were no signs of excess irradiation.

The patient was given roentgen ray irradiation, 200 r daily for 10 days, followed by 300 r for nine days, for a total of 4,700 r.

Examination shows a white and pliable scar with some telangiectasia from radiation coursing through it, at the site of the previous epithelioma. The whole face is pitted to a moderate degree from acne. The skin of the entire face is somewhat dry and tight. There is no other evidence of radiation sequelae.

DISCUSSION

Dr. Anthony C. Cipollaro: I am glad to have the opportunity of seeing this case, for several reasons. It indicates that conservative therapy can cure even a grade 4 squamous cell epithelioma of the lip in a region where extensive surgery would have been mutilating. The patient has remained well for 10 years, which fact shows that the therapy which was instituted has been effective. Third, I wonder, like those who wondered when the case was first presented, whether the previous radiation had something to do with the lesion, and I am inclined to believe that it did, with a rapidly growing squamous cell epithelioma in a young person. Tonight the patient has dryness of the skin, wrinkling and perhaps telangiectasia and changes in pigmentation, all of which are associated with overirradiation. It is well to bear in mind that unusual nodular lesions in a skin which has been irradiated, even though the surrounding skin appears only lightly affected, may be those of epithelioma of high grade malignancy.

Dr. George C. Andrews: I second the remarks of Dr. Cipollaro. In addition, many people believe that one should not treat cancer arising in a radiodermatitis by giving further roentgen irradiation. That rule, like all rules, should once in a while be broken. As a general thing, it is better to use some other form of treatment in a cancer produced by roentgen rays. In an epithelioma on or near the nose, surgical treatment may produce great deformity. I have seen other cases similar to this one treated by roentgen rays, with excellent cosmetic results, and cured for 10 years or longer.

Chronic Lymphedema of the Face. Presented by DR. GERALD F. MACHACEK.

M. B., a woman aged 28, was born in Venezuela and had always lived there prior to her entry into this country early in 1948. She had always enjoyed good health until one year prior to admission, in June 1948, when swelling of the soft tissues appeared about both eyes. After a few months the swelling about the right eye largely disappeared, but that about the left eye persisted and has spread to involve the left side of the face, including the cheek, left side of the nose and left half of the lips. While in Venezuela she received injections of penicillin from which she derived some benefit. There is a history of urticaria two years previously and of sneezing attacks in the early summer, lasting for about one month. Four or five years ago the patient had an infection in the left ear. She takes cathartic pills every day (bassoran® [containing 87 per cent sterculia gum and 8.7 per cent magnesium trisilicate] and veracolate® [a preparation containing phenolphthalein]).

The patient has been extensively studied in the medical service of the hospital. She has been seen by consultants from the ear, nose and throat, ophthalmology, dentistry, allergy and tropical medicine departments. Angioneurotic edema, dacryocystitis, Chagas' disease, onchocerciasis, filariasis and leprosy have been considered.

The Kline reaction of the blood was negative. The urine showed no albumin or sugar. Stool specimens revealed the presence of Giardia cysts and the ova of Ascaris, Endamoeba coli and Trichuris. The blood on several occasions showed relative leukopenia, with counts of 3,500, 4,360 and 2,880. The blood picture was otherwise normal. There was no significant eosinophilia. Roentgenologic examination of the chest, soft tissues of the face (for calcification), skull and paranasal sinuses showed no abnormalities. Throat cultures were negative for hemolytic streptococci, but a few colonies of these organisms were isolated on nasal culture. Agglutination tests for Brucella abortus were negative. Smear and culture from the antrums showed no growth. Two nasal smears were negative for acid-fast organisms. Two blood smears were negative for trypanosomes. Three young rats and two guinea pigs inoculated intraperitoneally revealed no trypanosomes after several weeks. A complement fixation test carried out by the United States Public Health Service at Bethesda, Md., was negative for trypanosomiasis. Cutaneous tests with filariasis antigen, brucellergen, Frei antigen and old tuberculin were negative. No microfilarias were found in the examination of 1 cc. of formaldehyde-treated blood. The basal metabolic rate was —12 per cent. Blood cholesterol was within normal limits. A neurologist considered that there was hypesthesia and hypalgesia below both elbows, more notable on the left in the ulnar nerve distribution, and that the ulnar nerve was slightly enlarged, but others were unable to confirm these observations.

Biopsies from the area of periorbital edema and from an enlarged lymph node in the left posterior cervical region were examined by a general pathologist and reported as showing only chronic inflammation.

While in the hospital the patient received 9,000,000 units of penicillin without apparent benefit. The Ascaris infection was successfully treated with hexylresorcinol. Numerous carious teeth associated with periapical infection were extracted. Antihistaminic drugs were tried without benefit. Edema subsequently developed in the right periorbital region but to a less extent. Two courses of roentgen ray treatments were administered to both sides of the face without benefit. Recently a lichenoid eruption developed on the neck and forehead. Several biopsies of skin from the last-mentioned lesions were done, but no specific pathologic changes were distinguished. Numerous mast cells were seen in some sections where

there were areas of chronic inflammation. Some sections showed what is evident clinically: edema and greatly dilated vessels, presumably lymphatics. Acid-fast staining, Fite and Ziehl-Neelsen, was done and showed no bacilli. A diagnosis of chronic inflammation and edema of the skin was made.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: I have battled with some of these cases and never done any good in any of them. I tracked down the cause in one patient to a possible intraocular angioma, and that person is now at the Mayo Clinic, where she is being studied and an intracranial operation is being considered. I have succeeded at times in reducing the swelling by using filtered roentgen irradiation to the area.

Lupus Erythematosus (Chronic Discoid); Cutaneous Leishmaniasis Scars. Presented by DR. GEORGE M. LEWIS.

DISCUSSION

DR. HOWARD FOX: The scarring is characteristic of oriental sore, of which I have seen numerous cases. The disease occasionally recurs and has been successfully treated by Drs. Dostrovsky and Sagher with grenz rays. In this type of the disease the histologic picture is different from that of oriental sore, as it shows a tuberculoid structure instead of the ordinary granuloma of leishmaniasis.

Atrophic Changes in the Hands Resembling Sclerodactylia, Associated with Myocardial Infarction. Presented by DR. GERALD F. MACHACEK.

N. S., aged 77, has presented symptoms of coronary insufficiency, with typical attacks of angina pectoris on exertion, since 1942. Symptoms of intermittent claudication, manifested by pains in the calves with exercise, have been present for about the same period. The blood pressure in 1942 was 180/90. Electrocardiographic studies at that time revealed a bundle branch block of unclassified type and a record which was indicative of myocardial damage and coronary sclerosis. In 1941 the patient began to note a burning sensation in the toes, and a little later the toe nails of the left foot became discolored, as did the nail on the left middle finger, and the latter became raised from its nail plate. Direct microscopic examinations showed the presence of fungi on several occasions, and Trichophyton rubrum was recovered by cultural methods. Since that time the patient has been treated with numerous fungicides and by having him pare down the affected nails with a glass slide.

At the present time the patient exhibits smooth atrophic skin on the hands and feet together with changes resembling sclerodactylia involving the terminal portions of the phalanges of the hands and feet. Recent blood pressure readings have been 200/110 and 200/98. There are moderate arteriosclerotic changes present in the fundi. Pulsations are absent in the dorsalis pedis and posterior tibial arteries bilaterally, but the radial pulses are easily palpable. The electrocardiogram now shows a left bundle branch block which is compatible with a clinical diagnosis of hypertensive heart disease.

The patient is presented as showing an example of peculiar disabling changes of the hands resembling sclerodactylia following myocardial infarction. This picture was found to occur in about 21 per cent of 178 cases by Alf C. Johnson. Similar cases have previously been shown by the presenter.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: It is not unusual to find such cutaneous changes in various forms of heart disease. Some years ago I studied a group of children with congenital heart disease with cutaneous changes varying from alteration in the temperature of the extremities to gangrene.

Chronic Porphyria with Poikilodermatomyositis. Presented by DR. GEORGE C. ANDREWS.
Epidermolysis Bullosa, Congenital Type (Associated Incontinentia Pigmenti and Follicular Atrophoderma)? Presented by DR. GERALD F. MACHACEK.
Pemphigus Vegetans Improved by Treatment with Aureomycin. Presented by DR. MAURICE J. COSTELLO.
Recurrent Herpes Simplex. Presented by DR. FRANK E. CORMIA.
A Case for Diagnosis: Cutaneous Leishmaniasis? Presented by DR. MAURICE J. COSTELLO.
Tuberculous Osteomyelitis. Presented by DR. MAURICE J. COSTELLO.
Pityriasis Rubra Pilaris. Presented by DR. GERALD F. MACHACEK.
A Case for Diagnosis: Verrucae Vulgares? Presented by DR. MAURICE J. COSTELLO.
Coccidioidomycosis. Presented by DR. MAURICE J. COSTELLO.
A Case for Diagnosis: Pemphigus Vulgaris? Treatment with Streptomycin. Presented by DR. MAURICE J. COSTELLO.

CLEVELAND DERMATOLOGICAL SOCIETY

Emerson Gillespie, M.D., *President*

Herbert H. Johnson, M.D., *Secretary*

Gerard A. DeOreo, M.D., *Reporter*

Oct. 27, 1949

Mycosis Fungoides, Tumor Stage, Improvement from Roentgen Therapy. Presented by DR. NORMAN ASEL, DR. PAUL CHIVINGTON and DR. WILLIAM SPILLER (service of DR. J. E. RAUSCHKOLB).

DISCUSSION

DR. E. W. NETHERTON: I should like to ask whether antimony tartrate has been tried by the members of the Society in treating cases of mycosis fungoides.

DR. B. LEVINE: I tried antimony potassium tartrate (tartar emetic) and then stibanose® (the diethylaminoethanol salt of sodium antimony gluconate). At first there was response; then the condition became stationary, and finally, worse. I found roentgen irradiation to be more effective. The response from antimony potassium tartrate was better than that from stibanose,® but the former drug was more toxic.

DR. E. B. HEISEL: At Ohio State University we have available P^{32}, or radioactive phosphorus. I have treated 1 patient with typical mycosis fungoides with doses of 4 millicuries of radioactive phosphorus; there has been a decided response in the pruritus, and many of the large nodules have become flattened.

A Case for Diagnosis: Lichen Ruber Moniliformis? Atypical Lichen Planus? Presented by DR. NORMAN ASEL, DR. PAUL CHIVINGTON and DR. WILLIAM SPILLER (service of DR. J. E. RAUSCHKOLB).

DISCUSSION

DR. H. N. COLE: There are some things about these lesions that did make one think of morbus moniliformis lichenoides. I think that that term, suggested by Wise and Rein, is preferable. However, the eruption on this patient is confined

mostly to the anterior aspect of one leg, whereas morbus moniliformis is usually comparatively symmetric and is a bead type of eruption in some places. There are photographs in Wise and Rein's article that show almost a replica of the picture seen in this patient. In addition, however, there are the beadlike arrangements, and this patient does not show that arrangement. She, too, has quite a bit of pruritus. Wise and Rein's patient did not have pruritus, and I believe Kaposi's patient did not have very much pruritus. I am inclined to think that this condition is probably a papular type of lichen planus.

DR. E. W. NETHERTON: I was under the impression that lichen ruber moniliformis was quite resistant to treatment. In this case the lesions practically disappear with roentgen ray therapy. Is that the case in lichen ruber moniliformis?

DR. NORMAN ASEL: When I first saw this woman the papular lesions were more raised than they are now. They were round and rather beadlike. I think that the lesions have responded somewhat to therapy and certainly are flatter than when first seen, although they are still present.

DR. E. W. NETHERTON: There was a section shown that had a very definite bandlike infiltration.

DR. E. H. JONES JR.: There are two previous biopsy sites which I think showed classic examples of lichen planus.

A Case for Diagnosis: Acanthosis Nigricans, Juvenile Type? Presented by DR. JOHN A. GAMMEL.

P. M., a 17 year old girl, about one year ago first noticed brown patches in the right groin, which lesions gradually increased in number and prominence.

She is the youngest of 5 siblings. Her parents are living and well. The patient had poliomyelitis in August 1944, leaving a foot drop and atrophy of the left leg.

When first examined in early June of 1949, the patient had about one dozen rough, brown patches in the right groin. They were slightly elevated and traversed by the normal furrows of the skin, the surface thus being given a papillary appearance. The largest lesion was 1 inch (2.5 cm.) in diameter. The patches were irregular in outline; some had sharp and others rather indistinct borders. Some newer lesions on the hip and thigh are barely perceptible macules.

The patient has numerous pigmented nevi of all shades.

The report on the biopsy, given by Dr. H. Z. Lund, was as follows: "The histologic sections showed a broad zone of short papillae covered by pigmented epidermis with slight hyperkeratosis. The keratin showed a 'basket weave' appearance in a rare focus. Mostly it was compact. The epidermis over the papillae was moderately hyperplastic in places and moderately thin in others.

"The lesions showed less hyperkeratosis and acanthosis than would an ordinary wart and were extended over a broader surface. Two diagnoses were considered: acanthosis nigricans and seborrheic keratosis. Against the latter was the fact that the epidermis was not decidedly hyperplastic and was not uniformly of the "basal" type of cell. In favor of the former was the varying degree of acanthosis and attenuation of epidermis. The lesion was more in keeping with acanthosis nigricans than with seborrheic keratosis. I did not think, however, that I could make an unqualified diagnosis of acanthosis nigricans without the aid of clinical observations.

"The diagnosis was papilloma of skin, consistent with acanthosis nigricans."

DISCUSSION

DR. G. A. DE OREO: In some cases acanthosis nigricans is unilateral, but the linear distribution in this case made me think of a linear type of neurodermatitis.

DR. J. R. DRIVER: I thought that the lesions were clinically rather characteristic of seborrheic verrucae. There was one rather elongated lesion, which looked like a scratch mark, superimposed on one of the lesions.

DR. H. J. PARKHURST: I am inclined to agree with Dr. Driver that this disorder may be a developing linear nevus.

DR. J. A. GAMMEL: I presented this case as possibly one of acanthosis nigricans of the juvenile type. If this patient had been older and if the lesions had been on the back and chest, I would have called the condition seborrheic verrucae. However, the unusual location and the age of the patient made me hesitate to accept that diagnosis, as also did the histologic report on it, although the histologic picture is not against it. The juvenile type of acanthosis nigricans may start unilaterally. The patient is acquiring more and more lesions. One little macule just appeared in the last week.

Congenital Defect of the Scalp and Left Eye. Presented by DR. ELDRED B. HEISEL, Ohio State University, Columbus, Ohio.

K. R., a white girl aged 4 months, was born with a malformation of the left eye and an eruption on the scalp. The mother stated that at birth the eruption on the scalp consisted of round to oval variously sized blisters. Since birth there has been no change in the eye, but some of the blisters have become flat, leaving bald spots; some have coalesced, and all have flattened somewhat. There has never been any associated inflammation, although a few blisters have had red centers. There is no history of any similar disturbance in the family. The mother had a series of furuncles during the third month of pregnancy.

Examination reveals a well developed and well nourished white infant, with normal observations on physical examination except with regard to the left eye and the scalp. There is a V-shaped defect of the left upper eyelid, involving the skin, conjunctiva and cartilaginous plate. Extending from the lateral commissure medially, over the lateral half of the cornea, there is a pseudopterygium. Aside from this defect, the eye was said to be normal by the attending ophthalmologist. When the patient was first observed, on July 28, 1949, the posterior third of the scalp was the site of approximately fifteen sharply circumscribed round to oval noninflammatory bullae, measuring 0.5 to 1.5 cm. in diameter. Three of the large bullae had coalesced to form a large bulla, measuring 1.5 by 3.5 cm. Most of the lesions were filled with clear serous fluid, but the fluid in a few was hemorrhagic. There were no hair follicles within the bullae.

The child was observed again on Oct. 10, 1949. There was no change in the left eye. Many of the smaller bullae had become flat, smooth, thin, atrophic spots. A few of these were shaped like inverted cones. The larger bullae had flattened but still contained fluid. In the center of one atrophic area there was a small collection of blood vessels. The borders of the bullae and the atrophic spots were slightly raised and cordlike. There were no hairs within the lesions, but roots of hairs which emerged outside of the spots could be seen through the thin epidermis covering the bullae and atrophic areas. The subcutaneous tissue was soft and thicker over the involved portion than on the rest of the scalp. On palpation of the atrophic spots, there appeared to be a defect in the underlying subcutaneous tissue, but the bony tissues were normal.

DISCUSSION

DR. H. N. COLE: It is unfortunate that we do not have a roentgenogram of the skull so that we might see whether there are any bone changes. I do not believe there is a possibility that these lesions might be secondary to amniotic adhesions, or so-called Simonart's bands. There is no hair in these areas. We have seen cases with defects in the skull which, peculiarly enough, will run through several generations and be in the same spot. I have never seen one with cystic character. Recently we observed a baby with a little area present on the top of the head at birth. This baby was not very old, and the arc was still bleeding, showing the Simonart band that had adhered to this spot, which was trimmed off at birth.

DR. E. B. HEISEL: I should like to say that all the lesions present now were present at birth. At birth all the lesions were bullae, or at least they contained fluid. The ophthalmologist expressed the opinion that the eye lesion was a congenital defect. In cutaneous defects of the scalp there are often other defects, such as we see in this case. This is the first baby of the parents. I will get roentgenograms and will attempt to present the baby again.

Generalized Nevoxanthoendothelioma. Presented by DR. ELDRED B. HEISEL, Ohio State University, Columbus, Ohio.

F. O., a white boy aged 11 months, was 4 months of age when I first observed him, on March 14, 1949. A small red papule appeared on the left shoulder, which was first noticed on Dec. 1, 1948, when he was at the age of 1 month. This lesion enlarged rapidly, and the eruption soon became generalized, involving the trunk and the scalp. All lesions began as red papules. As they developed in size, they became yellowish red. Aside from the cutaneous changes, the child was physically sound; his general health has been good and his development normal.

When first examined, this child presented ten to twelve lesions scattered over the scalp and trunk. They were noninflammatory and sharply limited and varied in size from papules 3 mm. in diameter to tumors measuring 1 by 1 by 1.5 cm. The largest of the lesions was on the left shoulder. It was covered with a crust, bled profusely with the slightest trauma and, except for its yellowish red color, had the appearance of a large granuloma pyogenicum. The child was observed the second time on Oct. 4, 1949. He presented more lesions, but the original ones had decreased in size. The yellow color in the lesions had become more prominent. At this time some of the lesions were definitely yellow and the lesions which were red revealed a yellow color on diascopic examination. Some of the tumors were firm; others were soft, but none were compressible.

Histologic examination of a specimen taken from one of the larger tumors was done by Dr. Fred Weidman. He reported that "the significant abnormalities appeared in the corium. All the normal collagenous tissue was replaced by a solid, diffuse mass of infiltrating cells. A few dilated capillaries ramified through the infiltrate, but on the whole the lesion was not outstandingly vascular.

"The infiltrating cells featured large numbers of small foreign body giant cells. The preponderant cell suggested a monocyte. Tiny vacuoles appeared within the cytoplasm in various places. Reasonably they were fatty, but the typical foam cell of xanthoma was not produced." Dr. Weidman concluded: "When one considers the combination of the clinical and histologic features, there appears to be little question that the condition is the nevoxanthoendothelioma of McDonough."

DISCUSSION

DR. H. N. COLE: This case is a very remarkable example of nevoxanthoendothelioma of McDonough. Ordinarily, these lesions clear up by themselves, without any treatment. In a matter of two or three years all the lesions will go away.

DR. E. B. HEISEL: Montgomery reported 2 cases and came to the conclusion that the condition was not an endothelioma but simply an endothelial type of lesion. He differentiated it from the juvenile xanthoma, for in this condition there is no increase in the blood lipids, whereas in juvenile xanthoma there is a definite increase in the blood lipids. We plan to obtain blood lipid studies on the parents and on the child and will report on them at the next meeting.

DR. J. H. SHEPARD: My son, aged 10, had such a lesion at birth, and the lesion is barely visible now. Blood lipid studies were done when he was at the age of 4 and again when he was 6, and the results of both were perfectly normal.

Multiple Idiopathic Hemorrhagic Sarcoma (Kaposi); Rhinophyma. Presented by DR. BENJAMIN P. PERSKY.

Keratosis Follicularis. Presented by DR. NORMAN ASEL, DR. PAUL CHIVINGTON and DR. WILLIAM SPILLER (service of DR. J. E. RAUSCHKOLB).

Parapsoriasis Guttata. Presented by DR. NORMAN ASEL, DR. PAUL CHIVINGTON and DR. WILLIAM SPILLER (service of DR. J. E. RAUSCHKOLB).

A Case for Diagnosis: Urticaria Pigmentosa? Neurotic Excoriations? Presented by DR. NORMAN ASEL, DR. PAUL CHIVINGTON and DR. WILLIAM SPILLER (service of DR. J. E. RAUSCHKOLB).

Epidermolysis Bullosa. Presented by DR. NORMAN ASEL, DR. PAUL CHIVINGTON and DR. WILLIAM SPILLER (service of DR. J. E. RAUSCHKOLB).

Emerson Gillespie, M.D., *President*

Herbert H. Johnson, M.D., *Secretary*

Gerard A. DeOreo, M.D., *Reporter*

Nov. 18, 1949

Cushing's Syndrome in a Negro Woman. Presented by DR. J. J. STEWART, DR. J. G. THOMSEN and DR. R. K. GARDNER (service of DR. H. N. COLE and DR. J. R. DRIVER), courtesy of DR. WILLIAM JEFFRIES, medical service.

DISCUSSION

DR. E. W. NETHERTON: A few years ago I presented before this Society a man who had a desquamated dermatophytosis. He also had a very typical Cushing's syndrome. After an adrenal tumor was removed, all his nails, which had previously been infected with fungus, cleared spontaneously, and they have remained normal since.

DR. WILLIAM JEFFRIES (by invitation): I have not seen any association of fungous disease with adrenal abnormality. The only endocrine condition in which I have seen fungous disease with any significant occurrence is hypoparathyroidism. My associates and I had occasion to see six children with hypoparathyroidism who had associated moniliasis of the nails.

Pemphigus Vegetans. Presented by DR. R. K. GARNER, DR. J. J. STEWART and DR. J. G. THOMSEN (service of DR. H. N. COLE and DR. J. R. DRIVER).

The patient, a 50 year old Negro woman, was presented on Sept. 22, 1949, with the diagnosis of a possible Behcet's syndrome. Since that time, the patient has acquired a generalized bullous eruption involving the mucous membrane and skin. The areas of maceration present vegetative lesions.

Recent laboratory observations showed large numbers of white blood cells in the urine. The hemogram showed an increase in eosinophils to 19 per cent of a 4,550 total white cell count; the total protein was 4.9 Gm. per 100 cc. of serum, with a 1.4 ratio of albumin to globulin.

The patient has failed to respond to the administration of carbarsone but is showing slight improvement after receiving 1 Gm. of aureomycin daily.

Histologic examination of skin from the inner aspect of the proximal part of the thigh showed a picture consistent with early pemphigus vegetans.

DISCUSSION

DR. J. R. DRIVER: I wonder whether or not we should call this pemphigus vulgaris rather than pemphigus vegetans. I was unable to find many of the vegetative type of lesions today.

DR. H. N. COLE JR.: Her condition has changed considerably since she began receiving aureomycin. She definitely had vegetative changes a few weeks ago in the axillas and groins, before receiving the aureomycin. Today she shows an entirely different appearance.

DR. G. M. STROUD: I should like to ask the presenters about her general course since the aureomycin was given.

DR. J. J. STEWART: This patient a few weeks ago had bullae around the eyes, nose and mouth and large bullae over the trunk and breasts and in the axillas. Since that time she has been receiving aureomycin and local therapy of starch baths and compresses and her condition has changed considerably. Her general condition is poor, the worst that it has been. As far as the skin is concerned, it is much better now. The patient can eat now, and the character of the lesions around the eyes, nose and mouth has changed remarkably.

Parapsoriasis en Plaque; Angiokeratoma (Fordyce). Presented by DR. ALLEN E. WALKER.

J. Z., a 65 year old plumber, noted the onset of a red, scaling eruption on the forearms and legs approximately four years ago. The eruption has tended to grow more prominent in recent years but never fades or disappears. The eruption burns during hot weather but is never pruritic. The patient takes no medicine.

His general health has been excellent. He has had a tendency toward low blood pressure for many years. No other members of his family have or have had a skin eruption.

On the volar and medial aspects of the forearms and medial aspects of the thighs and the popliteal regions of the legs, as well as the back and lower part of the abdomen, are discrete, very fine erythematosquamous plaques, varying from 1 to 15 cm. in diameter. The lesions are very superficial, and some resemble stains of the skin. In some areas on the lower extremities there is a tendency toward linear configuration. There is a tendency toward symmetry of the lesions; the skin exhibits a tache cérébrale. On the scrotum are numerous elevated, pinhead-sized red papules, soft and compressible. Other findings on physical examination were not remarkable except for a blood pressure of 122/64.

Urinalysis revealed no abnormality. The hemogram was normal.

A histological examination revealed a collection of cells in the corium consisting of lymphocytes and large, pale, poorly defined cells having large ovoid nuclei in which the chromatin was finely punctate. These large pale cells were presumably reticuloendothelial cells. In these regions also were numerous thin-walled vascular channels, which were lined by prominent endothelial cells.

The appearance was that of a nonspecific chronic dermatitis. The appearance was consistent with parapsoriasis en plaque. However, it is not possible to exclude an early stage of mycosis fungoides.

The patient has received roentgen therapy (50 r) to one plaque on the forearm, which has not been of benefit. He has been applying an aluminum acetate ointment nightly, with some apparent decrease in scaling of the lesions.

A Case for Diagnosis: Parapsoriasis en Plaque? Presented by DR. E. W. NETHERTON.

H. J., an unmarried Negro aged 21, is presented because of an eruption of two years' duration. In 1948 he contracted gonorrhea. Otherwise his past history is irrelevant. The lesions first appeared on the arms and gradually began to develop on the trunk and legs. They start either as a group of small blisters, which soon develop into scaly plaques, or as flat papules with large, loosely adherent scales. There has been no itching.

At present there are large and small serpiginous and rounded superficial scaly plaques disseminated over the trunk and extremities. The larger lesions show central clearing, with slight depigmentation. A large portion of the periphery of each lesion is covered with large, loosely adherent scales. Where scaling is absent the margins of the lesions consist of groups of closely placed flat, angular papules or pseudopapules caused by the accentuation of the normal markings of the skin. The lesions are not infiltrated. There are no vesicles present, and during our observation of this patient vesicles have not been observed.

The Wassermann and Kahn reactions of the blood were both negative. The fasting blood sugar level was 87 mg. per 100 cc. The hemogram and results of urinalysis were normal. Hyphae were not found in the scales.

Topical remedies have not been beneficial.

Tissue sections of biopsy material removed from the margin of an annular plaque showed the following observations: There was slight hypertrophy of the epidermis. Acanthosis was absent. There was a fairly dense layer of hyperkeratosis scattered over the epidermis. A parakeratotic layer, composed of four to six layers of cells, was noted. The granular layer was intact. There was pigmentation of the basal layer. There were a few small focal areas of a mild inflammatory reaction in the upper portion of the epidermis and an infiltrate consisting of lymphocytes and fixed tissue cells in the corium. There were a few focal areas of subepidermal edema with infiltration by lymphocytes.

DISCUSSION OF PRECEDING THREE CASES

DR. H. J. PARKHURST: In the second case, I could see the angiomas but I did not see angiokeratomas. I did not see any keratosis present there. In the last case I had difficulty in agreeing with the diagnosis of parapsoriasis. I felt that the lesions and their distribution in this case resembled very closely those we saw last month in a Negro presented as representing a case of psoriasis, and I felt we must consider the possibility that this eruption is psoriatic.

DR. H. N. COLE: In regard to the last case, I do not see how you could call that a case of psoriasis, even microscopically. It shows none of the abscesses in the epidermis, and I do not think it is psoriasis. However, I do not know whether or not I would agree with the diagnosis of parapsoriasis either. It is true that there is not very much to see, but in erythroderma figuratum perstans one sometimes does not see a great deal either, and I should be more in favor of that diagnosis. It is well known that the lesions may persist for a long period before changing.

DR. H. N. COLE JR.: In the first case, the plaques are certainly well defined and in some areas there is the suggestion of retiform parapsoriasis to which Crocker gave the name of parakeratosis variegata.

DR. A. E. WALKER: In the second case, I showed the histologic section to Dr. Lund, at first not telling him anything about the case, and he stated that it looked somewhat similar to acrodermatitis atrophicans chronica. In Gans' book much is made of some atrophy in cases of parapsoriasis that is very similar to this acrodermatitis.

DR. E. W. NETHERTON: In regard to the case of H. J., we had a good deal of difficulty in making a diagnosis. We considered psoriasis, and the annular centrifugal erythema which I think Dr. Cole had in mind was considered, as were parapsoriasis and sarcoidosis, but the biopsy showed hardly any of the changes compatible with the diagnosis of psoriasis. Clinically, the lesions do not have the edematous margin that is seen in the migrating erythema. Furthermore, the lesions are heavily scaled and more or less stationary and progress very slowly. I do not think the case is a classic one of parapsoriasis, and I shall have to follow it further. The condition has not responded to any treatment. There are no nail changes, no scalp lesions and no lesions with the classic distribution for psoriasis. I think further observation would be necessary to decide what the patient really has.

A Case for Diagnosis: Lichen Planus Keloidiformis? Presented by DR. R. K. GARDNER, DR. J. J. STEWART and DR. J. G. THOMSEN (service of DR. H. N. COLE and DR. J. R. DRIVER).

J. L., a white man aged 55, has had a pruritic, slowly enlarging lesion on the lateral aspect of the left leg for 15 years. When he was 8 years old, both legs and feet were burned by hot cinders. The present lesion lies within the involved area and is said to have begun as a small red, pruritic area; it has gradually enlarged peripherally. Pruritus is severe at times, and occasionally the lesion has been excoriated to the point of bleeding. There has been no involvement elsewhere, except for a slightly pruritic eruption on the left forearm during the past few weeks. The patient has taken bromide-quinine compounds for many years for colds; he denies the use of other drugs.

He is presently being treated for toxic adenoma of the thyroid, thyrotoxic heart disease, mild diabetes mellitus and polycythemia vera.

The past and family histories are noncontributory.

On the lateral aspect of the lower half of the left leg is a firm, elevated palm-sized plaque with an irregular, slightly hyperpigmented border. Its surface is flat, smooth, dry and reddish purple, with several small areas which appear pale and slightly depressed. There are a few small excoriations on the dorsum of the left forearm.

Histological examination showed dense fibrosis of the cutis. There were no hair follicles, and the sweat glands were scattered and dilated. In the deeper portions some of the arteries showed intimal proliferation and moderate stenosis. Superficially beneath the epidermis there was a zone of capillary proliferation of fibroblasts. A striking feature was intracellular edema of the basal layer and a broad separation of epidermis and dermis in many sites. The epidermis was hyperplastic; the granular layer was well developed, and the stratum corneum was of about average thickness and compact.

The patient is receiving digitoxin and small doses of insulin. He recently received a course of radioactive iodine for his thyroid disease. The skin lesion has not been treated.

DISCUSSION

DR. H. G. MISKJIAN: I do not agree with the diagnosis of a keloidal syndrome. May I ask Dr. Stewart whether the histological picture was of keloid?

DR. J. J. STEWART: It was not. I asked Dr. Lund, and he examined the section, covering the upper part with a piece of paper, and thought it looked like keloid. He removed the piece of paper, and the section looked like lichen planus. Sutton and Sutton stated that there is a type of lichen planus in which there are keloidal changes.

DR. H. G. MISKJIAN: In a German handbook there is mention of a lichen planus morphoeicus and lichen planus keloidiformis. The description is of small areas and not a big plaque like this.

DR. I. L. SCHONBERG: I feel that this is certainly some form of lichen planus, and microscopically there certainly is enough evidence regarding the infiltrate. In addition, the patient presented on the dorsum of the left middle finger a discrete, shiny papule, which was pruritic, and several lesions on the forearm which were highly suggestive of lichen planus.

Poikiloderma Atrophicans Vasculare. Presented by DR. GEORGE M. STROUD.

M. S., a 35 year old grocery cashier, is presented because of a pruritic plaque on the left shoulder and arthritic changes in her hands.

Since the age of 12 she has had four or five attacks of generalized arthritis. The last attack occurred in 1944, when she was bedridden for many months. During this time she was given neoarsphenamine intravenously. During this treatment she acquired dermatitis of the back of the hands, forearms and neck. This was treated with dehydrocholic-acid (decholin®) and one injection of BAL (2,3-dimercaptopropanol). After this eruption healed, a cyanotic change in the skin of the hands was noticed. This was increased by cold weather. The arthritis became inactive, and the chief residue was stiffening and deformity of the finger joints.

About a year and a half ago the patient noticed an itchy plaque above the left clavicle and also on the medial aspects of the forearms, particularly the right. The former has progressed in size, but the latter is almost healed.

Examination shows her to be healthy, except for slight hirsutism of the face and skin and bone changes.

There is a slightly depressed, mottled brownish red scaly plaque with a central "beaten silver" appearance, measuring 5 by 8 cm., above the medial portion of the left clavicle. It is very slightly indurated, and the blood vessels are slightly dilated. On the medial aspects of each forearm are slight redness and scaling, particularly on the right. The fingers are deformed, at the joints particularly, and are stiff. The skin over the finger joints is red, indurated and shiny. There is scaling on the tips of the fingers, which are a dusky red and cold. The toes show similar changes.

Immersion of the right hand in cool water produced aching of the fingers and made them more cyanotic.

The hemogram was normal except for a white blood cell count of 11,000 and a differential count of 74 per cent polymorphonuclear cells, 16 per cent lymphocytes, 5 per cent monocytes, 4 per cent eosinophils and 1 per cent basophils. A repeat white blood cell count one week later was 5,700. The sedimentation rate was 2.5 mm. per five minute period (the upper limit of normal is 1 mm.). The results of urinalysis were normal.

A section of skin from the left shoulder lesion showed slight hyperkeratosis and irregular acanthosis. A few sweat glands and ducts were present. The basal layer was intact, except for a few areas where there had been erosion by edema fluid. In the papillary part of the corium there was a dense infiltrate of mononuclear cells, with a moderate number of chromatophores, containing dark brown pigment, scattered in the infiltrate. The vessels of the corium were moderately dilated. The corium was irregularly quite thin, and some of the collagen was edematous, showing hyalinization in a few places deep in the corium.

The patient has taken 50 mg. of mixed tocopherols four times a day for the past 2½ weeks. Otherwise there has been no treatment.

DISCUSSION

DR. H. J. PARKHURST: Considering the tendency toward flushing of the face and the arthritic symptoms in the extremities, I felt that one would have to consider the possibility of subacute disseminated lupus erythematosus, which will possibly become acute.

DR. J. R. DRIVER: I thought of the same thing. Another thing I thought rather striking was that the lesion on the side of the neck was flattened on one side. Where the patient's dress covered up the skin there was none of the lesion, and I wondered whether or not there might be a light-sensitive factor which would go with lupus erythematosus.

DR. H. N. COLE: The patient told me that if she plunged her hands into cold water they went through the gamut of Raynaud's phenomenon.

DR. E. W. NETHERTON: I had seen this woman four or five years ago at the Cleveland Clinic, at which time she was being treated for arthritis under Dr. Hayden's care. He gave her neoarsphenamine, and she acquired an arsenical dermatitis. This cleared up, and the lesion seen today in the supraclavicular region has developed since. The patient did have the arthritis prior to the cutaneous lesions. She does have the pain and edema such as one would see in acrosclerosis. The possibility of lupus erythematosus certainly has to be considered. The question is whether the two conditions are related or separate.

DR. B. P. PERSKY: The question of whether poikiloderma atrophicans vasculare is a primary disease in itself or merely a symptom complex of some profound underlying disease has not yet been settled. The disease is not the same as lupus erythematosus, either clinically or histologically; in lupus erythematosus changes in the epidermis are rather definite and characteristic, while in poikiloderma vasculare atrophicans they are not. I believe the changes in the corium of this patient's skin are likewise different from those of lupus erythematosus. I therefore agree with the presenter that this is a case of poikiloderma atrophicans vasculare and not of lupus erythematosus.

DR. G. M. STROUD: I am not able to decide in my own mind whether this is a case of poikiloderma or one of lupus erythematosus. I think it belongs in the group called collagen disease. I believe it would be a good case for cortisone therapy. In the *Proceedings of the Staff Meetings of the Mayo Clinic* last summer, Hench reported one case in which there was improvement with administration of cortisone.

DR. J. R. HASERICK: I received a letter today from Jordan Baehr in New York concerning cortisone. He stated that he has yet to find anyone who has responded primarily to cortisone who did not need a maintenance dose of it; after three or four days the patients had relapses if cortisone was withdrawn. We should not get our hopes up too high about its use.

Calcinosis Cutis. Presented by DR. JOHN W. CASHMAN, Senior Acting Surgeon, United States Public Health Service, through the courtesy of DR. H. N. COLE.

DISCUSSION

DR. H. N. COLE JR.: I do not think that there is much question that this is calcinosis universalis. It can be differentiated from gout by the fact that the crystals do not stop roentgen rays. Furthermore, the histological section bears out this diagnosis. If these were sodium crystals the diagnosis would be gout

There are several theories as to the cause of calcinosis. Robinson in 1923 suggested that the condition might be due to an increase in the phosphatase enzyme. In 1935 Wilson presented a case of a 63 year old woman in whom he felt that an endogenous hypervitaminosis D was the factor in producing the calcinosis. However, in most of these cases the serum calcium and phosphatase levels are normal. I believe that Sutton feels that calcinosis is very often associated with xanthomatosis. The condition starts out with xanthomatosis, and for one reason or another these calcium deposits occur.

Trichinosis. Presented by DR. R. K. GARDNER, DR. J. J. STEWART and DR. J. G. THOMSEN (service of DR. H. N. COLE and DR. J. R. DRIVER), from the Medical Service of University Hospitals.

B. J. W., a 20 year old Negro woman, noticed a pruritic skin eruption about the ears and face 10 days before her admission to University Hospital on Oct. 25, 1949. It spread gradually until at the time of admission there was a generalized scarlatiniform eruption and pronounced swelling of the face, especially of the eyelids. Two days before admission she acquired a sore throat, felt chilly and began to have soreness of the muscles of the neck, shoulders and arms, together with drowsiness, anorexia and malaise. There had been occasional headaches but no vomiting and not much fever; her throat symptoms were not severe.

About four or five days before the onset of this illness she and her husband had eaten pork, which was said to have been well cooked. She denied the use of drugs, except for an occasional headache tablet containing acetanilid, potassium bromide and acetylsalicylic acid, the last having been taken about four days prior to the present illness.

The patient's husband, who ate the same pork, has had no complaints. However, his eosinophil count increased from 3 to 12 per cent during a one week period of observation. The reaction of the Trichina agglutination test was negative.

The hemoglobin level was 10.2 Gm. per 100 cc., or 65 per cent of normal. The leukocyte count rose from 7,050 per cubic millimeter on admission to 24,000 two weeks later; it subsequently fell to 10,850. An eosinophil count of 29 per cent on admission rose to 48 per cent at the end of two weeks and subsequently fell to 19 per cent. The urogram was within normal limits. The total serum protein level was 6.5 Gm. per 100 cc.; the albumin fraction was 4.1, and the globulin fraction, 2.4 Gm. per 100 cc. The albumin-globulin ratio was 1.7. The Kline diagnostic and exclusion tests gave negative reactions. Stool examinations revealed no abnormality. On Nov. 8, 1949, the Trichina agglutination test gave a 2+ reaction. Spinal fluid examination revealed an essentially normal condition. On Nov. 2, 1949, a Trichina larva was isolated from the peripheral blood.

The electrocardiogram and roentgenogram of the chest were normal.

Histological examination of a section of gastrocnemius muscle showed a slight focal subacute myositis. No parasites were seen.

On Nov. 11, 1949, 3 cc. of tetrachlorethylene was given, but no larvae were found in the subsequent stools.

DISCUSSION

DR. B. LEVINE: I think that I should mention, for the information of many of the members here, that Dr. Kline a few years ago developed a serologic test for trichinosis which is 100 per cent specific, certainly far more accurate than skin tests.

DR. R. K. GARDNER: This patient had the agglutination test performed in Dr. Kline's office, and the reaction was 2+.

A Case for Diagnosis: Parapsoriasis (En Plaque)? Lichen Sclerosus et Atrophicus? Cavernous Hemangioma. Presented by DR. R. K. GARDNER, DR. J. J. STEWART and DR. J. G. THOMSEN (service of DR. H. N. COLE and DR. J. R. DRIVER).

Calcinosis Cutis. Presented by DR. JOHN W. CASHMAN, Senior Acting Surgeon, United States Public Health Service, through the courtesy of DR. H. N. COLE.

SAN FRANCISCO DERMATOLOGICAL SOCIETY

Robert A. Stewart, M.D., *President*

Rees B. Rees, M.D., *Secretary-Treasurer*

Oct. 28, 1949

Oral Pemphigus. Presented by DR. NORMAN EPSTEIN.

DISCUSSION

DR. NORMAN EPSTEIN: I am surprised that no one questioned the diagnosis. I don't know that one can make a diagnosis of pemphigus of the mouth without the observation of lesions on the skin.

Cutaneous Manifestations of Lymphoma. Presented by DR. NORMAN EPSTEIN.

A 35 year old woman first noticed a small elevation on her left cheek six years ago. This was removed with the electrodesiccating current. One and one-half years ago she noticed a purplish, macular, painless, nonpruritic dime-sized lesion on her left cheek. This spread to involve the rest of her face but responded to roentgen ray therapy over a period of three weeks. Other lesions developing about the same time persisted and gradually spread to involve the areas in which they are now present. Swellings have been noted in the groins and neck. One month ago the patient delivered a full term normal infant. She has had pain in the ankles and elbows for the past three weeks. For the past four months there has been pain and swelling of the eyes, and edema has been present in the lower extremities for several months. Laboratory observations on Oct. 14, 1949, included a white blood cell count of 6,100, with 72 per cent polymorphonuclear leukocytes, 36 per cent of the total count being nonfilamentous. There were 2 per cent eosinophils, 25 per cent lymphocytes and 1 per cent young lymphocytes. On October 24 the hemoglobin was 12.4 Gm. The packed cell volume was 37 cc. per cent. The erythrocyte count was 4,010,000 with 4,000 leukocytes, including 50 per cent polymorphonuclear leukocytes. There were 7 per cent nonfilamentous leukocytes, 1 per cent basophils, 46 per cent lymphocytes and 3 per cent monocytes; the erythrocytes appeared to be normal. The platelet count was normal. On October 27 the erythrocyte count was 3,680,000, with 2,700 leukocytes, including 43 per cent polymorphonuclear leukocytes, 9 per cent nonfilamentous. There were 2 per cent basophils, 49 per cent lymphocytes, 3 per cent monocytes and 1 per cent young lymphocytes. The platelet count was 140,000. Results of urinalysis showed a

specific gravity of 1.008, a p_H of 6, with 1 per cent albumin, no sugar or acetone and occasional clumps of round epithelial cells and urate crystals observed microscopically. A roentgenogram of the lungs demonstrated no disease. Uptake studies showed a high tumor uptake and a high bone marrow uptake of radioactive phosphorus. A biopsy specimen was taken on October 19. The patient received total body irradiation because there is less tendency toward bone marrow depression with it than with radioactive phosphorus. Such total irradiation was given on October 20, October 22 and October 24.

DR. FRANCES TORREY: Perhaps Dr. Graves can tell us about the radioactive phosphorus uptake test.

DR. ALFRED GRAVES (by invitation): The uptake over the neoplastic tissue was about four times as great as over normal tissue. For a good response, the roentgenologist desires to observe an uptake ten times as great as normal in the diseased tissue, as determined by the Geiger counter. The picture in the bone marrow taken this week probably is consistent with lymphatic leukemia or lymphosarcoma.

DR. GRANT MORROW: Would nitrogen mustard help?

DR. NORMAN EPSTEIN: The lesions spread very rapidly toward the end of the pregnancy. The diagnosis is lymphoblastoma, probably of the lymphosarcoma type. Originally, the bone marrow did not show leukemic changes, but I think the patient is undergoing a leukemic phase. Dr. B. V. A. Lowbeer has expressed the opinion that one can predict the response to radiation by the radioactive phosphorus uptake test. Those at the visible tumor clinic felt that it would be better to hold the nitrogen mustard in reserve in this case.

DR. HERMAN ALLINGTON: How can one give nitrogen mustard intra-arterially if the lesions are so generalized?

DR. FRANCES TORREY: Dr. Bierman has stated the opinion that the tumor tissue in lymphosarcoma pushes away the venous blood and selectively utilizes arterial blood.

DR. ROBERT LOFGREN: What is probably meant is that if the material is injected intra-arterially it will be taken directly to the tumor tissue rather than being put through the whole circulation as it would be if injected intravenously.

DR. FRANCES TORREY: That appears to be the case.

Chronic Streptococcic (?) Ulcer of Penis. Presented by DR. LEO M. COLUMBUS.

Mr. F. D., a 40 year old white man, is presented because of a nonhealing painless ulceration in the ventral coronal sulcus of the penis, of about ten months' duration. Results of dark field examination and reaction to serologic tests for syphilis have been negative. Donovan bodies were not found in tissue preparations. Observations on a smear and culture in May 1949 were reported as follows: "gram-positive organisms, streptococcic and staphylococcic." There is a history of one previous similar ulcer (at a different site in the coronal sulcus) about one year ago, which healed completely within a month with local therapy only. The patient has had no known venereal disease but does give a history of preceding recurrent prostatitis and urethritis.

The lesion consists of a shallow oval ulcer, 0.8 by 1.5 cm., with a firm, rolled border and a smooth, nonvascular base. The latter is covered by a scant, sticky, semipurulent-appearing discharge. There has been no associated regional adenopathy, and physical examination reveals no other abnormalities. A biopsy has not been performed to date.

Treatment has failed to produce significant change. The following measures have been tried: topical application of penicillin, repository administration of penicillin (approximately 3,000,000 units), applications of podophyllin, use of 5 per cent silver nitrate preparation, application of sulfathiazole-urea powder, curettage and cauterization and application of bacitracin ointment.

DISCUSSION

DR. JULIAN LUNSFORD: I suggest that the lesion be excised and that the wound be sutured. The tissue may then be examined histologically.

DR. ERVIN EPSTEIN: The possibility of malignant degeneration should not be overlooked in this patient.

Paraffinoma of the Arms with Granulomatous Lesions over the Elbows. Presented by DR. PAUL FASAL.

The patient, a 56 year old white woman, had in 1920 a series of injections of a paraffin preparation into her arms for cosmetic reasons. These injections were given by a lay woman of San Francisco who called herself an "oil dermatologist." Several hundred of these injections were given, with the use of local anesthesia, in one sitting. The treated areas were smooth and nice looking for a short time, but six months later the patient noticed that the injected masses did not stay where they were originally put but began to separate into lumps and to settle slowly according to gravity. During the last twenty years this condition has become progressively worse, leading to difficulty in moving the elbows and hands. Owing to the restriction in motion, the patient occasionally suffered burns on her forearms and elbows. Lately several draining lesions developed, some within previously burned areas.

Both forearms and arms are infiltrated by a hard mass, sharply demarcated toward the normal tissue. This infiltration begins with a tonguelike process in the middle of the upper arm and reaches to the wrist. The skin over both elbows is discolored and shows scars from burns. Over the left elbow there are several superficial granulomatous lesions from which an oily substance drains.

Histopathologic examination of such a lesion showed granulation tissue consisting of lymphocytes, plasma cells, histiocytes, fibroblasts, foreign body giant cells and newly formed capillaries. There were numerous oval and round cavities, containing oil or crystals, causing the characteristic Swiss cheese appearance. Around some of these cavities there were accumulations of polymorphonuclear leukocytes.

Therapeutic suggestions will be appreciated.

DISCUSSION

DR. HERMAN ALLINGTON: During the past year we have seen a patient recently treated with a preparation of vitamin E in oil for coronary artery disease. It was given by the patient himself, under his physician's direction, in the anterior surface of his thighs. Within six months plaquelike thickenings appeared and draining sinuses began to be noted. Microscopically the classic picture of paraffinoma was found.

DR. PAUL FASAL: The question of therapy in this case is rather difficult. I agree with Dr. Torrey that surgical procedures do not seem feasible, as practically the whole circumference of the upper extremities is deeply infiltrated. I noticed that a copious drainage of an oily substance started from the hole left after punch biopsy; I contemplate punching several more holes in the distal parts of

the forearms in order to increase the drainage, and I want to combine this therapy with hot baths.

As an interesting sideline I want to report that the "oil dermatologist" who made the injections was arrested and fined $600 for violation of the State Medical Act after treating more than 800 women in San Francisco.

Dermatopathic Lymphadenitis (Lipomelanotic Reticulosis of Lymph Node in a Case of Generalized Dermatitis). Presented by DR. REES B. REES and (by invitation) DR. EDWIN M. HAMLIN.

W. C., a 79 year old retired white man, was first seen on March 26, 1949, regarding a more or less generally distributed dermatitis. This had been present for three or four months. In 1948 he had had a different type of eruption, which was severest in his palms, with the presence of blisters. He was treated for this in Springfield, Ohio, and in Chicago and had received some relief from the use of white petrolatum and liquid petrolatum containing 12.5 per cent of starch and of talc. A trichophytin test with a dilution of 1:30 produced no reaction. The patient was given a superficial fractional roentgen ray treatment to the worst areas, and with the use of starch and sodium bicarbonate baths and mild sedation the condition improved to a considerable extent. The patient was seen at intervals for the next two months and then disappeared from observation. In July 1949 he was seen at home and found to be very miserable. With the use of plain mineral talc topically and of methapyrilene hydrochloride (histadyl®) with ephedrine four times daily by mouth the condition again improved considerably. The patient was not seen again until Sept. 28, 1949.

At that time he was found to have huge axillary and inguinal lymph nodes. The condition had all flared two weeks previously, although it had never cleared. Punch biopsy of the skin of the left side of the abdomen revealed chronic inflammatory changes only. The patient was placed on treatment with vitamin A, 100,000 units daily, and somagen® (a protein carbohydrate, yeast, liver and vitamin B complex mixture) 3 drachms (12 Gm.) three times daily. Pyrrolazote® (8-pyrrolidinoethyl phenothiazine hydrochloride) 50 mg., was given four times daily. The patient was given another short course of superficial fractional roentgen ray treatment. In all he has had 450 r. Because of lymphorrhea following extirpation of a lymph node in his right axilla, he was given 150 r with filtration of 1 mm. of aluminum to that area. Histologic examination of the lymph node showed almost complete obliteration of the normal architectural pattern by a high degree of proliferative activity. No true lymphoid follicles remain. Throughout the node there are large pale areas of reticulum cell hyperplasia, the individual cells being large, pale staining and polyhedral. These have very large basophilic, irregular nuclei. The degree of pleomorphism is not pronounced, and no abnormal mitotic figures are seen. The sinusoids are engorged with blood. No capsular infiltration is present. In the pale-staining areas of reticular hyperplasia melanotic pigmentation has been laid down. Fat stains were not done, and stains for differentiating melanin from hemosiderin were not employed. The diagnosis on the lymph node was lipomelanotic reticular hyperplasia, by Dr. Jesse L. Carr.

Other laboratory observations, including the results of urinalysis, the hemogram and the results of bone marrow study were essentially normal.

DISCUSSION

DR. REES B. REES: This phenomenon is an accompaniment of long-standing pruritic dermatoses with considerable excoriation, although it does not occur in

all such cases. I do not know what this patient had originally, but the condition now appears to be a combination of generalized neurodermatitis and malnutrition. It has improved during the past ten days while the patient has been taking protein preparation given orally.

Vaccinia of the Eyelids (Herpes Simplex?). Presented by DR. CHARLES S. LINCOLN JR.

E. J., a 24 year old white girl employed as a nurses' aid, first acquired vesicles on the upper and lower eyelids on Oct. 21, 1949. The patient's roommate had been vaccinated three days previously. At that time the roommate also had herpes simplex of her left upper lip. The cowpox vaccination resulted in an immune reaction. The patient had washed out a uniform, the sleeve of which had been in direct contact with the roommate's vaccination site. The patient has had allergic eczema, which cleared six or eight years ago. There has been some dryness and scaling of the scalp and face during the past few months. The patient was given complete bed rest for pulmonary tuberculosis from 1945 to 1947. Treatment has consisted of aureomycin eye drops, as well as 250 mg. of aureomycin given four times daily by mouth, and 2 cc. of human immune serum globulin (Cutter) administered intramuscularly. Virus studies are being made. Photographs were taken.

DISCUSSION

DR. PAUL FASAL: Several months ago I saw a young woman with disseminated neurodermatitis who, after taking care of her freshly vaccinated baby, broke out in generalized vaccinia. Her general condition was poor; she had a high fever and was highly toxic. Under chloramphenicol (chloromycetin) medication she made a most dramatic recovery.

DR. FRANCES KEDDIE: I believe the condition is herpes simplex. This patient had been vaccinated four years previously and had an accelerated reaction. Her roommate, who now has an accelerated reaction had herpes simplex before the vaccination.

A Case for Diagnosis. Presented by DR. EDWARD J. RINGROSE.

E. H., a 12 year old white girl, first noticed lesions on the back of her left leg about two years ago. These gradually extended anteriorly and up to the thigh and lower part of the buttock. There are punctate red pepper spots and slivers over the entire left lower extremity from the ankle to the lower portion of the buttock. These fade on pressure. Histologic examination showed dilated capillaries in the papillary cutis. There has been no treatment.

DISCUSSION

DR. CHARLES MCNITT: The distribution is unilateral up from the ankle along the back of one leg and on the thigh. I believe the condition is a vascular nevus.

DR. FRANCES TORREY: I believe it is a vascular nevus.

DR. HERMAN ALLINGTON: This disorder appears to fit the description of angioma serpiginosum.

DR. REES B. REES: I agree with Dr. Allington.

DR. EDWARD RINGROSE: This condition probably is a vascular nevus.

A Case of Psoriasis Resistant to Treatment. Presented by DR. ALBERT SHUMATE.
Parapsoriasis en Plaques? Presented by DR. FRANCES A. TORREY.
A Case for Diagnosis: Lupus Vulgaris? Nonspecific Granulomatous Changes? Presented by DR. KEMP DOWDY.

A Case for Diagnosis: Infectious Eczematoid Dermatitis of the Ears? Presented (by invitation) by DR. ALFRED GRAVES.

Necrobiosis Lipoidica Diabeticorum of the Leg. Presented by DR. REES B. REES and (by invitation) DR. EDWIN M. HAMLIN.

Late Coccidioidomycosis. Presented by DR. EDWARD J. RINGROSE.

Robert A. Stewart, M.D., *President*

Rees B. Rees, M.D., *Secretary-Treasurer*

Dec. 16, 1949

Congenital Ichthyosiform Erythroderma. Presented by DR. FRANCES A TORREY.

F. C. R., a 5 year old white girl, was studied in the University of California Hospital from Nov. 15 to Nov. 22, 1949. There was normal gestation and birth, but when the child was at the age of 3 weeks a weeping red dermatitis developed under the chin and about the neck. This was treated with sulfathiazole ointment. It progressed and by the time the child had reached the age of 4½ months involved the entire body. Desquamation began early in its course. There has been very little change since that time. The general health has not suffered although the child has a chronic conjunctivitis and ectropion, bilaterally. According to the parents, histological examination by a physician in the past showed a condition compatible with psoriasis. The patient is a fairly well nourished child with generalized erythematous desquamating dry dermatitis. Laboratory and diagnostic procedures resulted in normal observations on blood count and urinalysis. Serum iodine was 5.2 micrograms per 100 cc. (normal, 4 to 8). The bone age was normal as determined by studies with roentgen rays. A blood serologic test for syphilis gave negative reactions. A culture from the eye showed hemolytic Staphylococcus aureus, nonhemolytic Staphylococcus albus and rare green-producing Streptococcus. Treatment has included avoidance of soap and water and the use of a soap substitute. Vitamin A has been given orally in a dose of 25,000 units daily, and the child has used vitamin A ointment topically. A histological section is presented.

DISCUSSION

DR. EDWARD RINGROSE: This condition looks like psoriasis, both histologically and because of the finger nail changes.

DR. FREDERICK NOVY JR.: I agree with the diagnosis of congenital ichthyosiform erythroderma. I recall two childhood friends of mine who had similar disturbances and who were treated with thyroid extract over a long period. The process tended to clear when they were in their twenties, and by the time they were 30 years old it was clinically well.

DR. FRANCES A. TORREY: This disturbance began at the age of 3 weeks, a characteristic unusual for psoriasis. The overgrowth of the nails is compatible with the diagnosis as offered. The lesions in the flexures are unusual in other forms of ichthyosis and in psoriasis. In another patient time and the administration of vitamin A seemed to clear the disturbance. This patient is receiving vitamin A by mouth and in ointment form. Laboratory observations and bone age were normal. There were no other significant medical observations. The condition is improving. The patient has been treated from time to time in the past for psoriasis without success.

Chronic Granuloma. Presented (by invitation) by DR. RALPH BEHLING.

M. C., a 43 year old white woman, was first seen at the University of California Dermatology Clinic on Nov. 16, 1949. There was a history of gradual progression upward from the lower extremities of lesions which had been present intermittently for 14 years. They began as simple erythema and progressed to form papules, nodules and ulcers, with crusting and healing. This process resulted in superficial scarring but no atrophy of the subcutaneous tissue. In 1931 a diagnosis of incipient pulmonary tuberculosis was made, but the disease did not materialize. The patient has also had rheumatoid arthritis for several years. She has never lived in a rural area.

Multiple pale scars, 1 to 2 cm. in diameter, are visible with moderate surrounding pigmentation. There is active ulceration of the left thigh and axilla. A vesicular eruption on an erythematous base is present beneath the right breast. There is no adenopathy. Testing with tuberculin in dilutions of 1:1,000,000 and 1:500,000 provoked no reaction. The fasting blood sugar was 59 mg. per 100 cc. Roentgenologic examination revealed a rheumatoid thoracic spondylitis. There were hypertrophic degenerative changes of the lumbar part of the spine. The sedimentation rate was 37 mm. per hour. The blood count revealed a normal differential count, and a blood serologic test for syphilis gave a negative reaction. Stool examination for parasites showed no organisms. There has been no treatment. Microscopic slides are presented.

DISCUSSION

DR. ROBERT LOFGREN: This patient gives a history of having had dysentery about one year prior to the onset of her present trouble, which began about 14 years ago. Lesions of the lower legs have been described in association with ulcerative colitis. I believe that the skin lesions may be related to recurrent colitis.

DR. ERVIN EPSTEIN: If this condition were confined to the legs, I would be satisfied with the diagnosis of Bazin's disease. The lesions are similar to those which occur with colitis. When the lesions are confined to the legs in combination with colitis, the condition should clear with the use of sulfaguanidine.

DR. JULES KEY: I think the diagnosis of Weber-Christian disease should be entered into the differential diagnosis. A new lesion is apparent on the left thigh and may well represent the primary type of lesion in this case. It is an erythematous, tender nodule. The patient states that her lesions start this way and also that she has been having an elevation of temperature at times to as high as 101 F. The biopsy did not show much fat tissue, and I believe a deeper biopsy would be worth while.

DR. GEORGE KULCHAR: Pyoderma gangrenosum is the name of the disease that has been described in connection with ulcerative colitis, and clinically the lesions tend to have an undermining effect. In the acute phase one can isolate hemolytic Staphylococcus aureus and microaerophilic Streptococcus from the lesions. The culture must be made under conditions of reduced oxygen tension.

DR. GEORGE WILSON: Meleney described recurrent chronic liquefying ulcers of the skin under the term "abacterial synergistic gangrene," which seems applicable to this case. Many of these cases responded to bacitracin wet dressings.

Poikiloderma of Civatte. Presented (by invitation) by LIEUTENANT COLONEL OSWALD R. JENSEN, MEDICAL CORPS.

R. S., a 20 year old white soldier, was hospitalized at Letterman General Hospital from Aug. 9 to Nov. 14, 1949, for treatment of disseminated neuro-

dermatitis. On admission it was noted he had a symmetrical brownish discoloration over all surfaces of his neck, shoulders, upper portion of the back and upper part of the chest. The affected areas showed a retiform arrangement of pigmentation with interspersed areas of depigmentation, atrophy and telangiectasia. According to the patient's mother, his skin was perfectly clear at birth but the disorder began in early childhood and has shown no change in its appearance to the present time. The patient denies ever having had any roentgen ray treatment to the involved area. Laboratory work, including blood count, urinalysis, serologic examination and chest roentgengram, revealed no abnormalities.

A biopsy was done. The Army Institute of Pathology reported on this biopsy as follows: "The changes in the section were not specific, but the focal atrophy of the epidermis and the presence of melanin pigment in the corium were consistent with the diagnosis of poikiloderma of Civatte. There was mild dilatation of the superficial capillaries, but the amount of inflammatory infiltrate was much less than is usually seen in poikiloderma of Civatte."

DISCUSSION

DR. PAUL FASAL: This is a most interesting case, and I agree with the diagnosis. Some authors do not consider poikiloderma reticulare of Civatte an entity but consider it a localized form of poikiloderma atrophicans vasculare of Jacobi. Others group it with Riehl's melanosis, as did Civatte himself 12 years after describing it as an entity. The younger Riehl saw this case during his visit to San Francisco and said that he felt sure that it was not a case of Riehl's melanosis. He stated the opinion that it was poikiloderma of Civatte.

DR. GEORGE KULCHAR: This is a poikiloderma-like disturbance, and it has been described as a result of excessive sun bathing in an article which appeared in the literature relatively recently. When this man was a child back in Ohio he was fond of sun bathing.

LIEUTENANT COLONEL ROBERT HIGDON (by invitation): The duration is unknown. The patient's mother informed us that the eruption was not present at birth and that it did begin in early childhood before the patient was extensively exposed to ultraviolet radiation in any form.

DR. KEMP DOWDY: This patient has a long history of atopic dermatitis, and at this time there is evidence of typical chronic lichenified atopic dermatitis involving the cubital fossae of the arms. The pigmentary changes appear to be superimposed on a similar lichenified atopic dermatitis of the neck region. The pigmentation in question is most likely the result of medicinal agents used in the past. The patient undoubtedly has had considerable roentgen ray therapy, which could account for the telangiectasia and possibly has some relation to the pigmentation; therefore, my diagnosis would be chronic atopic dermatitis with secondary pigmentary changes due to medicinal agents used.

DR. HERMAN ALLINGTON: I believe pseudoxanthoma elasticum should be considered and would suggest a deeper biopsy with elastic stains

LIEUTENANT COLONEL OSWALD R. JENSEN (by invitation): The patient presumably does have atopic dermatitis in addition to whatever other condition may be present. Pseudoxanthoma elasticum was considered, but there were no elastic tissue changes histologically.

Recalcitrant Pustular Eruption of the Soles. Presented by DR. REES B. REES and (by invitation) DR. EDWIN M. HAMLIN.

A Case for Diagnosis: Nodule on Nose. Presented by DR. MAX KRAUSE.

A Case for Diagnosis: Lymphangioma? Presented by DR. WILLIAM F. B. HARDING.

Hereditary Plantar Tylosis. Presented by DR. FRANCES KEDDIE.

LOS ANGELES DERMATOLOGICAL SOCIETY

Jud R. Scholtz, M.D., *President*

Molleurus Couperus, M.D., *Secretary*

Nov. 8, 1949

Favus in a 1 Year Old Girl. Presented by DR. HAROLD E. ANDERSON.

DISCUSSION

DR. J. WALTER WILSON: This child's mother was presented before this Society several years ago, before she was married. At that time we were aware of the fact that she had acquired the disease in childhood from her mother, and she in turn from her mother; now there are at least three generations, probably four, with the disease. Even if we could cure the child, I don't see how we could expect her to remain cured as long as the mother furnishes spores in the environment. The mother has had all the treatment she cares to have. All the cases we have had of favus in this locality have been tracted directly back to the Mediterranean area or eastern Europe except possibly the one in Santa Ana observed by Dr. James Lynch.

DR. HAROLD ANDERSON: I presented this patient because of the rarity of this disease in this locality and because of known favus in three and probably four generations. The mother has already had roentgen ray epilation three times and is still extensively infected with favus, and so there is little hope for cure of her case. With the mother constantly infecting the child, it seems there is very little to do for the baby.

Depigmentation Following Application of Modified Benzyl Benzoate Lotion. Presented by DR. RALPH B. COOMBER (by invitation).

The family physician diagnosed the condition as scabies and prescribed benylate® (a modified benzyl benzoate lotion containing benzyl benzoate, 25 per cent) and also tripelennamine (pyribenzamine®) cream with dibucaine (nupercaine®). The dermatitis cleared, but depigmentation followed in the patches to which the medication had been applied. This depigmentation has remained essentially the same. Patch tests with tripelennamine cream with dibucaine gave negative reactions. Application of benylate® to a small area of the abdomen resulted in depigmentation at the site of application.

Examination shows patchy areas of depigmentation over the dorsal surface of each foot. There is also a small area of depigmentation over the lower left portion of the abdominal area, at the site of the application of benzyl benzoate, as well as on the tip of the right index finger, which was used in applying the medication.

DISCUSSION

DR. J. WALTER WILSON: If these areas of depigmentation prove to be permanent we should like to know the mechanism by which they appeared. If the condition is actually a result of the chemical application, I think we would all be interested to learn of such a chemical, i. e., one capable of permanently depigmenting skin. Negroes exposed to the monobenzyl ether of hydroquinone in the rubber industry become depigmented. As far as I can make out, all the areas in those cases become repigmented. The similarity between that chemical and benzyl benzoate can be seen by the structural formulas—the developers for developing films depend on the hydroquinone. I should not expect benzyl benzoate to do

anything to lessen pigmentation, and, if it actually does so, I do not believe the effect will be permanent.

DR. THOMAS H. STERNBERG: The simplest possible explanation for the depigmented areas and the most likely is that the patient is allergic to benzyl benzoate and that the resulting dermatitis is responsible for the leukoderma.

DR. RALPH B. COOMBER (by invitation): I told the patient to apply the ointment with her finger to an unexposed area, and when I saw her a week later there was very little inflammation but there was depigmentation of the finger and abdomen. I have found that benylate® is an aqueous solution but that, in order for it to be made an emulsion, triethanolamine stearate is used.

Sarcoid of Boeck. Presented by DR. H. C. L. LINDSAY.
Idiopathic Atrophy of the Skin. Presented by DR. SAMUEL AYRES JR. and DR. SAMUEL AYRES III (by invitation).
Granuloma Annulare. Presented by DR. M. E. OBERMAYER and DR. E. T. FOX (by invitation).
A Case for Diagnosis: Atopic Eczema? Presented by DR. L. H. WINER.
A Case for Diagnosis: Dermatofibroma? Von Recklinghausen's Disease? Presented by DR. L. F. X. WILHELM and DR. W. H. GOECKERMAN.
"Burning Tongue" Associated with Electrogalvanic Current of the Mouth. Presented by DR. SAMUEL AYRES JR. and DR. SAMUEL AYRES III (by invitation).
Lichen Planus with Nail Involvement. Presented by DR. SAMUEL AYRES JR. and DR. SAMUEL AYRES III (by invitation).
Vitiligo in Dermatomal Distribution. Presented by DR. JUD R. SCHOLTZ.
Erythema Induratum. Presented by DR. BEN A. NEWMAN.
A Case for Diagnosis: Pigmented Purpuric Lichenoid Dermatitis of Gougerot and Blum? Presented by DR. J. WALTER WILSON.
Nevus Unius Lateris. Presented by DR. GORDON MACDONALD.
Hypertrichosis of the "Nevoid" Type. Presented by DR. MAXIMILIAN OBERMAYER.

Jud R. Scholtz, M.D., *President*

Molleurus Couperus, M.D., *Secretary*

Dec. 13, 1949

Return of Hyperpigmented Skin to Normal, Complicated by Appearance of Vitiligo. Presented by DR. H. C. L. LINDSAY.
Dermatitis Medicamentosa of External Origin. Presented by DR. KENNETH L. STOUT.
Melanin Pigmentation of the Face. Presented by DR. JUD R. SCHOLTZ.
Urticaria Pigmentosa. Presented by DR. THOMAS H. STERNBERG and DR. DANIEL J. PERRY (by invitation).
Recurrent Leukoplakia Buccalis: Case Presented for Evaluation of Therapeutic Results. Presented by DR. J. WALTER WILSON.
Sarcoidosis. Presented by DR. PAUL D. FOSTER.
Nevus of Hair Follicle Origin (Nevus Syringocystadenomatosus Papilliferus). Presented by DR. PAUL D. FOSTER.
Trichophyton Purpureum Infection of Hands and Feet. Presented by DR. HARRY P. JACOBSON.
Coccidioidomycosis. Presented by DR. HARRY P. JACOBSON.

DETROIT DERMATOLOGICAL SOCIETY

Frank Stiles, M.D., *President*

Hermann Pinkus, M.D., *Recorder*

Nov. 16, 1949

Histoplasmosis Involving Tongue, Larynx, Lungs and Probably Liver. Presented by DR. FRANZ BLUMENTHAL and Dermatological Staff of Wayne County General Hospital, Eloise, Mich.

J. G., a 63 year old white man, acquired an ulcer of the tongue in December 1948. Later he became hoarse and lost 7 pounds (3 Kg.). When first seen he

presented a deep ulcer (1 by 1.5 cm.) on the anterior right side of the tongue. The liver was felt 8 cm. below the right costal margin. A biopsy of the tongue showed chronic granulomatous inflammation and bodies resembling Histoplasma capsulatum, and a liver biopsy showed miliary granulomas but no micro-organisms. H. capsulatum was isolated in cultures from tongue, stools and bronchial secretions. No acid-fast bacilli were found on repeated examinations. Guinea pig inoculation showed reticulum cell hyperplasia of the spleen.

Treatment consisted of the administration of copper sulfate, ¼ grain (15 mg.) three times daily and in 1:5,000 solution as a mouth wash. Penicillin, streptomycin, sulfadiazine and iodides given by mouth and intravenously were used. The ulcer has shown progressive healing since July 1949.

DISCUSSION

DR. EDWARD P. CAWLEY, Ann Arbor, Mich.: It may be very difficult at times to make the diagnosis of histoplasmosis, and it is essential that the causative organism be cultured from any patient suspected of having this disease before one concludes definitely that one is dealing with histoplasmosis. I understand that in this case H. capsulatum has been cultured from stool specimens. My associates and I have had approximately 15 cases of histoplasmosis at the University Hospital in Ann Arbor within the past few years, and in at least two instances the lesions were localized to one structure or organ.

DR. ARTHUR E. SCHILLER, Detroit: I wonder whether the roentgenogram of the chest was characteristic of histoplasmosis, because to me the roentgenogram seemed to be that of a chronic nonspecific bronchitis.

DR. EDWARD P. CAWLEY, Ann Arbor, Mich.: So far as I know there is not a typical roentgen picture for histoplasmosis, as it involves the lungs or any other part of the body.

DR. ISADORE BOTVINICK (by invitation): The patient lived in the Wayne County Infirmary, Eloise, Mich., for several years. He had been a foundry worker. On first admission, roentgenologic examination of the chest showed lesions which were interpreted as pneumonoconiosis. In spite of the close contact in which inmates live in the Infirmary, no other cases of histoplasmosis have been found there so far.

Blastomycosis of Skin and Prostate. Presented by DR. ISADORE BOTVINICK (by invitation).

E. L. B., a Negro aged 37, first acquired lesions on the nape of the neck in late December 1947. Soon afterwards more lesions appeared on the back and the right leg. In March 1948, because of acute urinary retention, the patient was hospitalized on the urologic service of another hospital. Before dermatological opinion was sought, he was treated with penicillin, streptomycin, oxophenarsine hydrochloride (mapharsen®) and sulfadiazine for 10 days. During this time a prostatic abscess drained into the urethra. A culture of the urine was reported as abacterial. The lesions gradually grew larger.

When first seen by me, on March 22, 1948, the patient had four granulomatous plaques, one each on the nape of the neck, the right knee, the right ankle and the back. A biopsy showed the typical features of blastomycosis including numerous organisms. A Blastomyces was recovered in cultures from the prostatic secretion and the lesion on the ankle. An intradermal test with Blastomyces vaccine obtained from Dr. Conant at Duke University produced erythema and slight edema in a zone 0.7 cm. in diameter. Roentgenologic examination of the chest showed a

small area of semiconsolidation in the right costophrenic angle on April 9, 1948, and repeatedly later until December 1948. In March 1949 the lungs were reported clear.

Treatment was with potassium iodide in increasing doses, roentgen rays, sodium iodide given intravenously and Blastomyces vaccine administered subcutaneously. A total of 40 Gm. of aureomycin was given by mouth between June 21 and July 11, 1949. There was no apparent response to this drug. Improvement has been slow, but steady, and the patient returned to work Aug. 30, 1949.

DISCUSSION

DR. ISADORE BOTVINICK (by invitation): The interesting features of this case are the isolation of Blastomyces from prostatic secretion, the lack of response to antibiotics, including aureomycin, and the good but slow response to very high doses of iodides in combination with Blastomyces vaccine. The patient now receives 10 Gm. of sodium iodide intravenously five times a week and takes 6 dessert spoonfuls (about 48 cc.) of saturated solution of potassium iodide daily by mouth.

Lupus Erythematosus of Face and Generalized Nodular Lesions of Tuberculid Type. Presented by DR. FRANZ BLUMENTHAL.

D. W., a white man aged 25, acquired skin lesions in 1944 while he was in New Hampshire serving in the United States Navy. Lesions were noted on chest and back. When transferred to Cuba, the patient acquired lesions on the face. He was treated at several Navy hospitals, and a biopsy obtained from the face in 1945 was diagnosed as lupus erythematosus.

He was first seen by me in March 1948, when he presented bluish red, well defined, slightly infiltrated lesions on the cheeks, lips and forehead. Similar lesions were noted on the arms and in the infrascapular region. Some of the lesions were scarred and atrophic. The patient responded well to injections of a gold preparation.

At the present time he has two active lesions on the left side of the face and residual atrophy and scars at the sites of healed deep nodular lesions. He has some nodular lesions with central necrosis scattered over the trunk and legs.

Roentgenologic examination of the chest showed no evidence of pulmonary tuberculosis.

DISCUSSION

DR. HERMANN PINKUS, Monroe, Mich.: At this time, the patient presents two distinctly different types of lesions. He has two red, somewhat atrophic plaques on the face which are clinically typical of discoid lupus erythematosus. The lesions on his arms and trunk, however, would be very unusual manifestations of lupus erythematosus. There are deep cutaneous nodules, some of which ulcerate. The active lesions and the residual scars form a pattern which corresponds to the old picture of livedo racemosa. Years ago such cases were thought to be on a syphilitic or tuberculous basis, and this patient's condition resembles closely a case which was published from J. Jadassohn's department as an instance of atypical tuberculids (Pinkus, H.: *Arch. f. Dermat. u. Syph.* **170**:194, 1934). Goldschlag and Chwalibogowski (Über einen Fall von Periarteritis nodosa mit ausgebreiteten Hauterscheinungen, *Arch. f. Dermat. u. Syph.* **171**:622, 1935) later pointed out that my case probably was one of periarteritis nodosa, and in retrospect I agree with them. I suggest that this man here also has skin manifestations of periarteritis nodosa. A biopsy from one of the active nodular lesions and studies of tuberculin sensitivity would be helpful.

Arsenical Keratoses of Palms and Soles in a Diabetic Woman with Carcinoma of the Breast. Presented by DR. FRANZ BLUMENTHAL and Dermatological Staff of Wayne County General Hospital, Eloise, Mich.

Ichthyosis in a 3½ Year Old Child, Decidedly Improved with Vitamin A Therapy. Presented by DR. FRANZ BLUMENTHAL and Dermatological Staff of Wayne County General Hospital, Eloise, Mich.

Three Cases of Varicosities, Ulcers and Lymphedema of Legs Treated Surgically. Presented by DR. FRANZ BLUMENTHAL and Dermatological Staff of Wayne County General Hospital, Eloise, Mich.

Kaposi's Hemorrhagic Pigmented Sarcoma and Hidradenitis Suppurativa. Presented by DR. FRANZ BLUMENTHAL and Dermatological Staff of Wayne County General Hospital, Eloise, Mich.

Chilblain Lupus of Besnier-Hutchinson. Presented by DR. FRANZ BLUMENTHAL and Dermatological Staff of Wayne County General Hospital, Eloise, Mich.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Captain Robert L. Gilman (MC) USN, *Chairman*

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Nov. 18, 1949

A Case for Diagnosis: Lupus Erythematosus? Dermatomyositis? Parapsoriasis en Plaque (Pathologic Diagnosis of the Thigh Lesion).

Presented by DR. M. H. SAMITZ and (by invitation) DR. J. ALBOM.

H. C., a white man aged 48 years, well developed but showing obvious loss of weight, presents a dusky erythematous and edematous plaquelike appearance of the face. The skin of the back and the sides of the neck above the collar bone exhibit a reticulated erythema. The skin of the external ears is red and scaly. The plaques present minimal telangiectasia, no scaling and no atrophy. There is an erythematous scaly eruption of the elbows in the olecranon region. There are erythema and edema of the fingers. The patient was well until nine months ago, when he acquired (1) a "pins and needles" type of sensation involving the fourth and fifth fingers of both hands, shooting down from both elbows and appearing only when the elbows were bent, (2) migratory muscular and arthritic pains, (3) blotching erythema of the face, ears and neck and (4) loss of weight of 52 pounds (24 Kg.) associated with weakness.

The patient weighs 160½ pounds (73 Kg.). He presents slightly enlarged, discrete nodes in both axillas and numerous shotty subcutaneous nodules, some of which are also noted in the upper extremities. There is questionable hepatomegaly. The fingers are slightly and diffusely swollen.

Roentgenograms of both knees showed moderate osteoarthritis; no abnormalities were observed for the skull and spine, and both hands showed several small cystic areas with reactive sclerosis suggestive of possible sarcoidosis. However, neurofibromatosis should be considered, as well as early rheumatoid type arthritis. The "full mouth" showed no apparent foci of infection. The chest was normal.

An electrocardiogram done on June 21, 1949, gave normal readings. Otolaryngologic examination revealed normal sinuses, that the tonsils had been surgically removed and that the ears were normal. A smear taken from both nares was negative for Hansen's bacillus. The Kahn reaction of the blood for syphilis was negative on May 27, June 28 and July 17, 1949. Stool cultures were negative. Urinalysis gave results within normal limits. Total proteins were 6.2 Gm., 3:7:1, on May 26, 1949, and 5.8 Gm., 2:4:1, on June 28, 1949. Creatinine was 0.112 Gm. per 119 cc. A blood culture was negative. The blood uric acid was 2.4 mg. per 100 cc. of blood. The fasting blood sugar was 103.4 per cent. Agglutination tests for brucellosis, typhus and typhoid were negative on June 22, 1949.

The sedimentation rate was as follows: on May 27, 1949, 19 mm. per 30 minutes; on June 27, 1949, 24 mm. per 30 minutes; on Oct. 5, 1949, 103 mm. per hour, and on Oct. 12, 1949, 111 mm. per hour.

As to the hemogram, in 10 examinations, extending over a period of five months, the only significant abnormality was (1) a white cell count of 2,400 found one month ago (otherwise there was not a leukopenia) and (2) mild anemia.

Bone marrow studies gave the following data: July 26, 1949—"mild myeloid hyperplasia; no L. E. Cells seen," and Aug. 18, 1949—"sternal puncture negative; no L. E. cells seen."

On Oct. 26, 1949, the blood urea nitrogen was 9 mg., and the creatinine, 1 mg. per cent.

Report on the biopsy (nodule from forearm) was "multiple neurofibroma." Specimens of skin and muscle of the left forearm, and a lymph node from the left axilla were reported as normal; a subcutaneous nodule from the left arm was reported as showing a mild inflammatory reaction of the fat tissue.

The patient has been treated with bismuth injections (seven), penicillin administered daily for two weeks, bismuth sodium triglycollamate (bistrimate®) given orally for five weeks, acetylsalicylic acid, ascorbic acid and quinine sulfate, as well as supportive measures.

DISCUSSION

DR. E. R. GROSS: I think it is difficult to rule out a diagnosis of seborrheic dermatitis. The lesions on the face are very suggestive. The patient has pronounced seborrhea of the scalp and lesions on the elbows. Regarding the lesions on the hands, this man had been a truck driver for some years prior to taking up his present occupation of grocer. He stated that his hands have always been in contact with gasoline, and he now has contact with defatting agents, puts his hands into pickle jars and so on; I think he has a contact dermatitis of his hands.

DR. VAUGHN C. GARNER: I agree with Dr. Gross in his interpretation of this condition.

DR. D. M. SIDLICK: So do I.

DR. MORRIS MARKOWITZ: There is no reason why the patient should not have one or two diseases at the same time. I examined the subcutaneous lesions on the forearms and those on the abdomen, and they looked like nonsuppurative panniculitis.

DR. SAMUEL R. KAUFMAN, Wilkes-Barre, Pa.: Has porphyrin been studied in this case?

DR. M. H. SAMITZ: This case is a real problem, and the question was whether it was dermatomyositis or subacute lupus erythematosus. If we evaluate the features clinically here and read O'Leary's fine description of dermatomyositis and Keil's report in the *Annals of Internal Medicine* (**16**:828, 1942) we can correlate the clinical features that this patient shows with the clinical features of dermatomyositis. Unfortunately, we have never been able to get a biopsy to confirm that diagnosis. I think we never chose the correct spot. We should have selected the pectoral muscle or some of the muscle tissue up around the shoulder, which would have been of more help to us. The low white cell count and the sedimentation rate would fit in with subacute lupus erythematosus or dermatomyositis. What impresses me is the peculiar periorbital swelling and the livid color of the face, which are more or less pathognomonic of dermatomyositis. We did not test the patient for photosensitivity or for porphyrin. I believe the joint pains and the scaly lesions are part of the picture of dermatomyositis.

Progeria. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. MERLE HAANES.

F. F., a white boy aged 3 years, after a full term, normal delivery, at 7 weeks acquired apparent arthritis of the left hip. This was treated with traction, penicillin and aspiration. At the age of 9 months the hair fell out and the child walked with a peculiar gait. The scalp veins remained prominent. At the time of hospitalization cutaneous changes were present on the abdomen and back and were described as being thickened plaques. The latter changes have now disappeared. Changes in the toe nails appeared at a later date. At the age of 2 years the child had seven teeth. At present he has 13. The anterior fontanel has not closed. The present weight is 24 pounds (11 Kg.). The patient is very alert mentally.

The skin of the abdomen has a slight lumpy appearance, but no nodules are palpable. There is a retiform pattern of hyperpigmentation and depigmentation. The hair of the scalp is sparse and coarse. The toe nails are dystrophic. There are only 13 teeth that show normal occlusion. The vascular pattern of the scalp is prominent. The finger joints are prominent, with some limitation of motion.

The blood pressure was 85/60, and the temperature, normal The neurological examination revealed no abnormality. The fundi, lens and scleras were normal, as were the nasopharynx and ears. The cardiovascular system revealed no abnormality, nor did the genitals.

A complete blood count was within normal limits. The blood urea nitrogen was 12 mg. per cent. The fasting blood sugar was 73 mg. per cent; phosphatase, 6.9 mg. per cent, and cholesterol, 199 mg. per cent; flocculation and thymol turbidity were normal. The bleeding and clotting time were normal. The serologic tests for syphilis gave negative reactions. A test with purified protein derivative for tuberculosis gave negative reactions. The electrocardiogram showed changes suggestive of coronary artery disease. Roentgenograms of the skull revealed no abnormality. Roentgenograms of the hands showed a bone age of 2 years and 3 months. There was erosion of the terminal phalanges in both hands. A roentgenogram of the spine showed nothing abnormal.

DISCUSSION

DR. H. H. PERLMAN: I thought the condition Weech's disease at first, but it has not the characteristic features. However, the child does have an increase of intracranial pressure, of which the large vein of the scalp is evidence. Also the fontanel, which should be closed at this age, is wide open.

DR. VAUGHN C. GARNER: It is interesting that the boy appears to show hypotension, rather than hypertension, as one would normally expect in this condition.

DR. E. R. GROSS: Dr. Wright and I had the opportunity to observe this youngster at the age of 6 months. It was our impression that he had widespread scleroderma.

DR. MERLE HAANES: This patient was admitted to the pediatric service at the University Hospital and studied thoroughly. He provides an interesting problem, but we had great difficulty in classification. His disorder did not fit into the ectodermodysplasia group. The teeth are not deformed, although the occlusion is very poor. There are only 13 teeth, and there should be about 22. The condition did not fit into classification as Rothman's or Werner's syndrome. The question is, what will be the outcome? The prognosis probably is very poor.

Bowen's Disease of the Glans Penis. Presented by DR. M. H. SAMITZ and (by invitation) DR. PRIMO MORI.

F. McG., a Negro aged 52 years, well developed and well nourished, presents on the glans penis a firm, indurated, bright red, painless quarter dollar–sized plaque involving the external meatus and the frenulum. The border of the lesion is hyperpigmented. There are scars over both inguinal areas. The inguinal nodes on the left are slightly enlarged. The patient had gonorrhea at the age of 21 years and four to five times since then, the last attack having been five years ago. He has had urethral stricture for the past 20 years. He underwent treatment for latent syphilis 10 years ago.

The blood pressure was 140/90. The hearing is diminished. The patient has intermittent bouts of paroxysmal tachycardia.

A complete blood count revealed only a slight lymphocytosis. The sedimentation rate was 38 mm. per hour; the blood sugar, 89 mg., and the blood urea nitrogen, 11 mg. The serologic tests for syphilis gave negative reactions. Results of urinalysis were within normal limits except for the presence of 3 to 5 leukocytes per high power field. The electrocardiogram showed myocardial damage due to coronary artery disease. A roentgenogram of the chest revealed moderate generalized cardiac enlargement and moderate elongation, tortuosity and widening of the aorta.

A biopsy specimen examined by Dr. Beerman in February 1949 was reported as showing Bowen's disease.

The patient has been treated with local application of 0.045 Gm. of neoarsphenamine locally since June 17, 1949, with no apparent change in the lesion.

DISCUSSION

DR. HERMAN BEERMAN: Clinically I would not call this lesion Bowen's disease. I thought it more like erythroplasia of Queyrat.

DR. FRED D. WEIDMAN: I do not think there is any clash. I think that the more of these cases we see, the more erythroplasia resolves itself into intraepidermal cancer, whether simply that or progressing on to the dyskeratotic cytologic picture that is called Bowen's disease. I should not be surprised if vacuolated cells were found some day in some of these cases of erythroplasia of Queyrat and the condition would go on to resemble Paget's disease of the skin. Cases like this are valuable in crystallizing our ideas as to the fundamental nature of erythroplasia.

DR. M. H. SAMITZ: This man is the second of two patients with Bowen's disease in whom we have tried Dr. Sachs's local therapy with neoarsphenamine. In the first case of this disease that I presented, several years ago, there was a fairly good result from the local application of neoarsphenamine in a man with erythroplasia of Queyrat.

Gumma of the Right Side of the Face; Noduloulcerative Syphilis of the Arms; Asymptomatic Neurosyphilis. Presented by DR. M. H. SAMITZ and (by invitation) DR. R. REFOWICH.

S. C., a Negro aged 55 years, who denies previous serious illnesses or venereal disease, presents a firm, fluctuant, painless, walnut-sized mass in the right parotid area. On the extensor surface of the right arm, just proximal to the elbow, there is a painless ulcer with a necrotic slough and undermined borders and surrounded by induration and pigmentation. On the left side there is a somewhat similar lesion. The patient is separated from his wife. He had one son about

35 years ago who died at the age of 6 months—cause of death not known. No history of tuberculosis, cancer or diabetes could be elicited. For the past four months the patient has noticed firm, painless nodules just proximal to each elbow on the extensor surface of the arms. About two weeks after the onset these nodules began to break down and ulcerate. The only treatment the patient used prior to entering the hospital was application of hydrogen peroxide. Two months ago he first noticed a painless "bump" on the right side of his jaw over the parotid area; this became progressively larger until on admission he was barely able to open his mouth. From 1942 to 1947 he worked as a bartender. The patient states that he had serologic tests for syphilis every six months during that time and all gave negative reactions.

The patient has hypertension; his blood pressure was 190/100. He has lost 28 pounds (13 Kg.) during the past two years.

Results of urinalysis were within normal limits. Smears and cultures of pus revealed no acid-fast organisms but nonhemolytic Staphylococcus albus. A complete blood count showed 66 per cent hemoglobin, 3,900,000 erythrocytes and 8,800 leukocytes, with 70 per cent polymophonuclear leukocytes, 29 per cent lymphocytes and 1 per cent monocytes. A serologic test for syphilis gave positive reactions (4+) with 128 units, repeated once. Examination of the cerebrospinal fluid revealed protein, 75 mg. per 100 cc.; colloidal gold curve, 2233332000; a positive Wassermann reaction, and no cells. A roentgenogram of the lungs showed slight pulmonary fibrosis and emphysema. A tuberculin test with purified protein derivative no. 1 gave a negative reaction.

Report on the biopsy was as follows: "The specimen of skin examined revealed an epidermis that was within normal limits. There was, however, an increase in pigment in the basal cell layer. The upper part of the cutis showed some edema and a scattering of lymphocytes. In the remainder of the corium there were foci of inflammatory cells, many collected about blood vessels, composed mainly of lymphocytes and plasma cells. In some areas the blood vessels were thickened; a few were occluded. In the subcutaneous tissue there was an invasion of the fat by lymphocytes and an occasional plasma cell, eosinophil and epithelioid cell. No organisms were seen. The pathological diagnosis was probable syphilis" (H. Beerman).

The patient has been treated with procaine penicillin (aqueous), 300,000 units twice a day, for 10 days; boric acid compresses, twice a day, and bland ointment locally. The ulcers of the arms have decreased in size and are much cleaner, with very little slough remaining. The mass over the parotid gland has decreased to half its original size.

DISCUSSION

DR. HERMAN BEERMAN: It is surprising that everybody accepts the diagnosis of syphilis. When this section was presented in our Clinicopathologic Conference, everybody doubted the diagnosis, especially since the man had bilateral lesions.

DR. JOSEPH V. KLAUDER: I should like to challenge the diagnosis of gumma on the right side of the face. The lesion does not feel like one. It seems attached to the bone. Despite the fact that the patient had 3,000,000 units of penicillin almost a month ago, with half reduction in size of the lesion, I would predict that it will not completely disappear. One may see such lesions as those he presents on the arms in sites subject to trauma. For example, one will see a bilateral nodulo-ulcerative tertiary syphilid appearing on both knees in a scrubwoman. On areas subject to trauma one may see bilateral syphilids (Klauder, J. V.: Syphilis and Trauma, *J. A. M. A.* **78**:1029-1037, 1922).

DR. M. H. SAMITZ: I was about to explain that this man is a bartender and usually stands at the bar with pressure on his elbows, and we feel that this trauma is a contributory factor. A roentgenogram was taken of the lesion on the jaw, and there is no relation of this lesion to any bony structure. This man finished his antisyphilitic therapy about four days ago, and the lesion has partially resolved.

Darier's Disease. Presented by DR. M. H. SAMITZ and (by invitation) DR. PRIMO MORI.
Lupus Miliaris Disseminatus Faciei. Presented by DR. M. H. SAMITZ.
A Case for Diagnosis: Morphea? Presented by DR. CARROLL S. WRIGHT and DR. E. R. GROSS.
Early Arthritis Associated with Psoriasis. Presented by DR. M. H. SAMITZ and (by invitation) DR. J. ALBOM.
Hemosiderosis (Schamberg's Disease)? Presented by DR. LOUIS GOLDSTEIN.
Acanthosis Nigricans. Presented by DR. LOUIS GOLDSTEIN.
Necrobiosis Lipoidica Diabeticorum Without Diabetes. Presented by DR. JOHN F. WILSON.
Necrobiosis Lipoidica Diabeticorum. Presented by DR. JOHN F. WILSON and (by invitation) DR. GEORGE P. ROUSE.
Noduloulcerative Syphilis. Presented by DR. M. H. SAMITZ and (by invitation) DR. R. REPOWICH.
Erythroderma; Exfoliative Dermatitis. Cause? Psoriasis? Presented by DR. M. H. SAMITZ and (by invitation) DR. J. ALBOM.
Purpura Annularis Telangiectodes (Majocchi's Disease) with Necrosis. Presented by DR. JOHN F. WILSON.
A Case for Diagnosis: Pemphigus? Dermatitis Herpetiformis? Bullous Lichen Planus? Presented by DR. M. H. SAMITZ and (by invitation) DR. J. ALBOM.

METROPOLITAN DERMATOLOGICAL SOCIETY

Joseph C. Amersbach, M.D., *President*

Valentine C. Baker, M.D., *Secretary*

Nov. 21, 1949

Bowen's Disease. Presented by DR. LESLIE PAXTON BARKER.

T. C., a Negro aged 38, in 1947 noticed a lesion on the glans penis near the frenulum. This caused no discomfort, and no treatment was instituted until he was hospitalized for repair of an inguinal hernia in May 1948. At that time he had a hard, verrucous growth on the glans penis about 2.5 cm. in diameter and elevated about 1 cm. above the surface. A biopsy of the lesion done at that time showed no evidence of malignant changes, and the lesion was removed with the electrocautery.

The patient entered the skin clinic at St. Luke's Hospital in October 1949. At that time he had a hyperkeratotic, slightly raised lesion on the left side of the glans, about 1 cm. in diameter. The periphery of the lesion seemed infiltrated. Blood serologic reactions were negative. Biopsy of a specimen from the margin of the lesion showed it to have the histological characteristics of Bowen's disease. There was no inguinal adenopathy present.

DISCUSSION

DR. WILLIAM H. HUBER: Clinically the lesion is an erythroplasia. This is the type of lesion which reveals histologically a Bowen-disease-like picture rather than the nonspecific balanitis described by Sachs as erythroplasia. It is not uncommon to see areas of atrophy and scarring associated with hypertrophic leukoplakia-like areas, as in this case. A biopsy should, of course, be performed.

DR. J. LOWRY MILLER: I think this is a real erythroplasia. There are two conditions which go under the name erythroplasia—one type which is successfully

treated by arsenic and another type which is definitely precancerous. This disorder is the latter. The lesions on the prepuce and the corona are erythroplasia. Only two lesions are active—the ulcer on the corona and a little ulceration on the glans. I would desiccate both.

DR. HARRY VAN VELSOR (by invitation): It is difficult to determine where the lesion ends and normal tissue begins. The lesion is indurated. Is it necessary to resort to midshaft amputation in order to provide future protection?

DR. ROYAL M. MONTGOMERY: I agree with Dr. Miller that desiccation is the best treatment. I showed a similar case before this Society on March 17, 1947 (ARCH. DERMAT. & SYPH. **58**:617 [Nov.] 1948), in which the lesion was desiccated by a urologist about one year ago. The result is very satisfactory.

DR. CARL T. NELSON: I agree this is a true erythroplasia—that is, Bowen's disease of the penis. It is not just a simple balanitis of the type which is said to respond to local applications of neoarsphenamine. Electrodesiccation rather than roentgen irradiation should be the treatment of choice here.

DR. LESLIE PAXTON BARKER: This is a precancerous, if not already cancerous, condition developing on sclerosing balanitis. I think a biopsy should be done from other areas when treatment is instituted. Roentgen therapy is definitely contraindicated for this type of lesion. It must be destroyed, and probably electrosurgical treatment or desiccation would be the best method.

DR. J. LOWRY MILLER: I agree that roentgen ray treatment is contraindicated.

Darier's Disease with Extreme Plantar Hyperkeratosis. Presented by DR. C. T. NELSON.

News and Comment

GENERAL NEWS

Space Available in Scientific Exhibit at Atlantic City.—Space is available in the Dermatological Section of the Scientific Exhibit at the Atlantic City Session of the American Medical Association, June 11 to 15, 1951. Applications for space should be sent immediately to Dr. James R. Webster, 122 South Michigan Avenue, Chicago 3.

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

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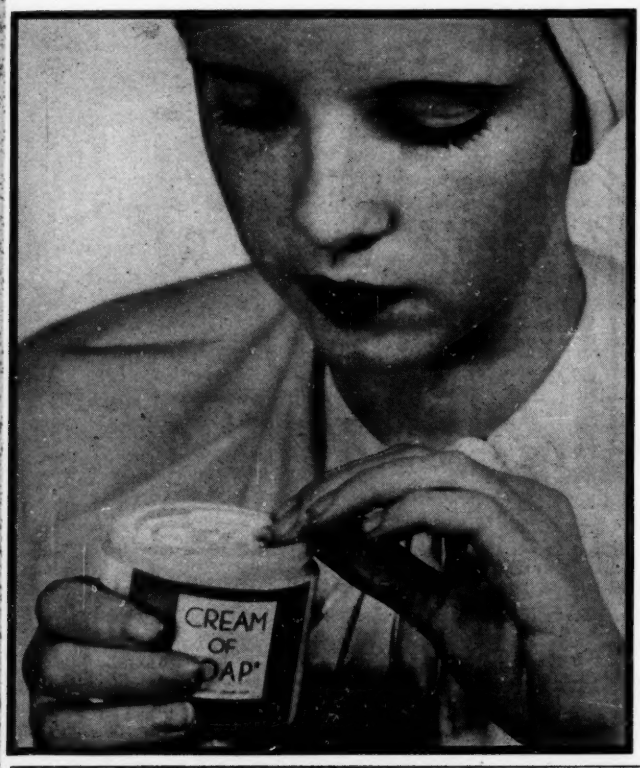

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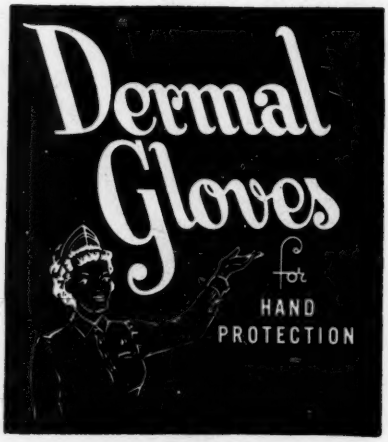

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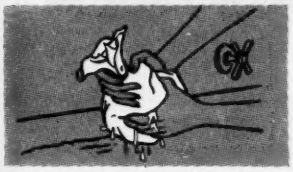

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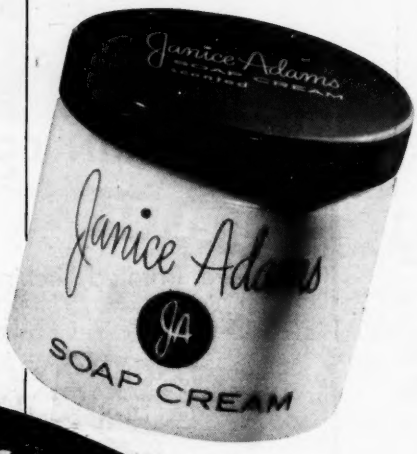

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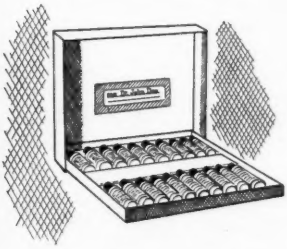

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